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Sexual dimorphism in the response to antidepressant therapy: Biological basis and clinical implications

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Abstract

Depression represents a complex mental health problem worldwide, affecting millions of people and causing significant societal and personal distress. A plethora of evidence has emerged indicating an important role of gender dimorphism in depression, with prevalence rates, symptomatology, and treatment responses differing between men and women. Women are generally more likely to suffer from depression, which is often attributed to hormonal influences, psychosocial stressors, and gender-specific coping mechanisms. In contrast, men may exhibit different depressive patterns, characterized by externalizing behaviors and higher suicide rates. Neurobiological studies highlight gender-specific differences in brain structure and function, as well as in neurotransmitter systems, which may impact treatment efficacy and response variability. While conventional pharmacotherapy remains pivotal, personalized approaches that integrate psychotherapeutic modalities such as cognitive-behavioral therapy and mindfulness-based interventions have increased in recent years. However, gender differences in treatment outcomes emphasize the need for differentiated, gender-sensitive clinical strategies. This review summarizes the current literature to highlight the complexity of depression and the importance of tailoring interventions to optimize clinical outcomes in diverse populations.

Key words: depression, gender dimorphism, sex differences, antidepressants

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Introduction

Depression represents a major topic in contemporary mental health discourse (1). It is widespread throughout the global population and has a profound negative impact on the well-being of individuals and the functioning of society. In the past two decades, research on depression has made significant progress and provided insights into its multifaceted nature, including the role of gender dimorphism in its manifestation and the increasing effectiveness of depression therapies (2).

The prevalence of depression underlines its status as a global health concern, with the World Health Organization (WHO) estimating that over 264 million people worldwide suffer from depression (1). However, numerous studies underline the importance of considering depression not only as a global phenomenon, but also as a psychiatric syndrome showing high variability across different patient populations (3). Additionally, gender dimorphism has been shown to be an important factor influencing the prevalence, symptoms and treatment outcomes of depression, with significant differences in prevalence and symptomatology found between men and women (4). Women are more prone to depression than men, a trend that is attributed to numerous factors including hormonal fluctuations, psychosocial stressors, and gender-specific coping mechanisms. Conversely, men may exhibit different patterns of depression characterized by externalizing behaviors, such as substance abuse, aggressiveness, and an increased risk of suicide, underscoring the importance of gender-specific approaches in understanding and treating depression (5). Various studies have shown gender-specific neurobiological correlates of depression that reveal different patterns in the brain structure, function and connectivity between men and women (6-10). The observed neurobiological differences could be the reason for the gender-specific differences in susceptibility to depression and response to treatment, and thus contribute to the development of personalized therapeutic approaches (11).

Traditional forms of therapy such as pharmacotherapy and psychotherapy continue to play a decisive role in the treatment of depression. In recent years, however, increasing emphasis has been placed on personalized and integrative therapy that takes individual needs and preferences into account (12). The evolving landscape of depression treatment reflects a paradigm shift towards multidimensional approaches that take into account the heterogeneity of depression symptoms and the different needs of those affected (13). These multidisciplinary approaches include pharmacotherapy as the cornerstone of depression treatment, using highly effective psychotherapeutic methods such as cognitive-behavioural therapy (CBT), interpersonal therapy (IPT), and mindfulness-based interventions (MBIs) (14). CBT is a structured, time-limited psychotherapeutic approach that focuses on the relationship between thoughts, feelings, and behaviors. The main goal is to recognize and change negative thought patterns and beliefs that play a prominent role and underlie emotional distress and maladaptive behaviors (15). CBT often includes practical strategies and techniques, such as cognitive restructuring and exposure therapy, to help patients in creating and maintaining healthier and positive thought patterns and coping mechanisms. IPT is an empirically-based form of

psychotherapy that focuses on social and emotional relationships between the patient and loved ones, co-workers and acquaintances. By addressing patients' relationship dynamics and communication skills, IPT as a therapeutic approach engages in improving social connections and affiliations, which, in combination with pharmacotherapy, could eventually lead to significant remission (16). MBIs incorporate practices such as meditation and focused breathing to promote awareness and acceptance of the present moment (14). These techniques help individuals to develop a non-judgmental attitude towards their thoughts and feelings, which can potentially reduce stress, anxiety and depressive symptoms. Importantly, the effectiveness of these interventions may vary by gender, which requires a nuanced understanding of gender-specific treatment responses and the integration of gender-specific strategies into clinical practice (15, 17).

Despite significant advances in the research and treatment of depression, considerable challenges remain. These include inequitable access to healthcare, lack of resources, the stigma and discrimination associated with mental illness, and urgent need for more targeted and efficient therapeutic interventions tailored to individual patient requirements (18, 19). The present review summarizes the latest research on depression, gender dimorphism, and antidepressant treatment effectiveness to provide a comprehensive understanding of the complexity of this mood disorder. Moreover, we provide an in-depth discussion of evidence-based strategies for prevention, diagnosis, and antidepressant treatment in diverse populations that could potentially help in developing innovative sex-specific therapeutic approaches in depression.

Depressive disorder – pathogenesis and symptomatology

Depression is a chronic, debilitating psychiatric disorder, influenced by genetic, epigenetic, endocrine and environmental risk factors (20, 21). The underlying pathological mechanisms remain unclear, although several theories have been established, including the monoaminergic hypothesis, hypothalamic-pituitary-adrenal (HPA) axis hypothesis, inflammatory hypothesis, and neuroplasticity hypothesis (22). The monoaminergic theory, which focuses on the roles of neurotransmitters such as serotonin, noradrenaline and dopamine and their depletion in the brain, is consistent with the mechanism of action of the main currently available antidepressants. Nevertheless, this hypothesis has its limitations, as approximately 50% of depressive patients experience relapse and show poor therapeutic response (23). The HPA axis hypothesis proposes a link between stress exposure and chronically elevated levels of cortisol and development and progression of depressive disorder (24). The inflammation hypothesis suggests a link between depression, cytokines and systemic immune activation (25). Importantly, multiple studies showed elevated levels of proinflammatory cytokines, such as interleukin 6 (IL-6), IL-10, IL-12 and tumor necrosis factor α (TNF-α) in patients suffering from depression (26). The neuroplasticity hypothesis posits a close relationship between the depressive phenotype and impaired neuronal survival, migration and synaptic formation and significant decline in neurogenesis, particularly in the hippocampus (27-29). Recent evidence indicates that

estrogen, particularly estradiol, plays a role in mood modulation, and reduced levels of this sex hormone have been linked to depression in women, especially after menopause (30). Research suggests that estrogen interacts with several neurotransmitter systems and influences behavioral and biochemical changes associated with mood disorders. Unexpectedly, excess estrogen may also exacerbate depressive symptoms, suggesting that careful regulation of estrogen levels and/or its receptors could be considered as a potential drug target, which may enhance therapeutic response in combination with antidepressants (30).

Depression is characterized by core symptoms such as sadness, anhedonia, irritability, feelings of worthlessness and guilt, difficulty concentrating, and neurovegetative changes, including significant appetite and sleep disturbances (31). Besides, depression is associated with increased risk for other psychiatric disorders, such as anxiety and substance abuse, and overall higher mortality rates from suicide (32). Patients suffering from depression also have an elevated risk of developing cardiovascular and/or metabolic disease, particularly coronary artery disease and type 2 diabetes (33, 34). Notably, depressive disorder has profound impact on the quality of life: this mental illness complicates management of several chronic diseases and contributes significantly to the global burden of disease and disability (33-35).

Gender-specific differences in the pathogenesis of depression

In discussing the role of sex and gender in brain physiology and disease, we tackle a complex and largely unexplored area of neuroscience. Neuroscientists have traditionally focused on studying the male brain and behavior, both in humans and experimental animals, which has led to significant gaps in knowledge regarding the female brain and sex differences (36-39).

Depression occurs almost twice more frequently in females compared to males over the course of their lives (40). Women suffer from prolonged and/or recurrent depressive episodes more frequently and experience more severe symptoms than men. In addition, women are more prone to weight gain, anxiety and more severe neurovegetative symptoms during depressive episodes (40, 41). One of the proposed mechanisms for these differences is related to sex hormones, particularly estrogen and progesterone. This mechanism assumes that the increase in the secretion of female sex hormones near puberty increases the incidence of depression at this stage of life in women compared to men. On the other hand, the incidence of depression in women after menopause, when the level of reproductive hormones stabilizes, is similar in women and men (42). Estrogen has significant interactions with serotonin in the brain, which may explain some of the differences in symptom presentation and response to pharmacotherapy between the sexes. Estrogen stimulates the production of serotonin by increasing tryptophan hydroxylase levels and enhances the sensitivity and expression of serotonin receptors, particularly 5-HT_{1A} and 5-HT_{2A} (43). Moreover, estrogen facilitates serotonin release at synapses, promotes neuroplasticity in the hippocampus, and interacts with other neurotransmitter systems, thereby influencing mood and cognition (43).

Another important mechanism is related to the differences in the functioning of the monoaminergic systems between the sexes. A deficiency in the serotonin precursor tryptophan leads to a temporary decline in serotonergic transmission in the female brain, resulting in significantly greater exacerbation of depressive symptoms in women compared to men suffering from this mental illness (44, 45). Furthermore, various studies in patients and experimental animals have shown gender-specific differences in serotonin synthesis and metabolism, as well as in the activity of other monoaminergic systems such as dopamine and noradrenaline (44-46). Differences in dopamine regulation were found, with women showing higher synaptic dopamine concentrations in the striatum compared to men. Additionally, age-related changes in serotonin and noradrenaline levels appear to be generally greater in women than in men (44, 45). All of the abovementioned physiological phenomena and differences between women and men could partly explain the dissimilarities in the pathogenesis of depression and symptom presentation in both sexes.

At the molecular and structural level, sex-specific differences in gene and protein expression, neurotransmission, brain structure, behavior, development and manifestations of psychiatric disorders and therapeutic drug response have been reported in both preclinical and clinical trials (47-56). Gonadal hormones, sex chromosomes, and external factors interact to influence sexual differentiation of the brain during prenatal development and later in life (57-60). Testosterone and estrogen play critical roles in the "masculinization" and "feminization" of the brain at key developmental stages, while changes in gonadal hormones throughout life continue to influence brain structure and function in both sexes (61-63). Dubol et al. (2021) conducted a systemic review, focused on investigating the impact of biological fluctuations of sex hormones throughout the menstrual cycle on neural circuits implicated in affective and cognitive functions. The authors performed a detailed and comprehensive analysis of 77 neuroimaging studies involving 1,304 naturally cycling and healthy women and reported that changes in female sex hormones across the cycle exert effects on the activity and structure of various brain regions, particularly the prefrontal cortex, anterior cingulate cortex, hippocampus, insula, amygdala and inferior parietal lobule (9). Notably, emerging evidence indicates an increase in the volume of gray matter in the hippocampus during periods of time characterized by high estrogen levels and functional studies show heightened activity in brain regions involved in emotional processing during the same periods (9). Moreover, a direct, positive association was observed between estradiol concentrations and gray matter volume in the hippocampus (9). Importantly, research confirmed that during periods in life characterized by substantial changes in levels of ovarian hormones and gonadotropins, such as pregnancy (64) and the (peri)menopausal transition (65), a significant decrease in hippocampal volume occurs. Taken together, these findings strongly suggest that physiological fluctuations in female sex hormones may alter the structure and signalling in cortico-limbic brain regions, possibly contributing to women´s enhanced susceptibility to depression (64, 65).

A study performed by Kundaković and Tickerhoof (2024) highlights the role of epigenetic mechanisms as one of the critical factors underlying sex-specific differences in brain structure, functions and behavior. In rodents, epigenetic changes such as DNA methylation and histone acetylation modify gene expression patterns in males and females in different ways, thus influencing neural circuitry, behavior and susceptibility to mental illness, including depression (42). In males, certain genes implicated in emotional processing and regulation show higher susceptibility to methylation, resulting in their reduced expression and impaired emotional control. This can lead to profound behavioural changes, including increased aggressive behavior and diminished ability to cope with stress (66). Conversely, elevated histone acetylation in specific brain regions has beneficial effects and enhances neuronal plasticity, allowing male rodents to better adapt to stressful stimuli (56). Importantly, evidence shows reduced DNA methylation of genes involved in emotional control in women, potentially reflected in greater emotional sensitivity and empathy (42). On the other hand, histone acetylation in women may provoke an increase in the expression of genes such as *BDNF*, *NR3C1* and *CRF*, which were previously associated with a protective role against stress and anxiety. Sex hormones show a close and bidirectional relationship with epigenetic mechanisms, thus affecting gene expression and behavioral phenotype and contributing to sex-specific differences (42). Testosterone in males can provoke epigenetic modifications associated with aggression, while estrogen in females induces changes that affect emotional processing and control (66). In addition, fluctuations in estrogen levels during the menstrual cycle can lead to changes in mood and behavior in women (42, 56). Understanding these mechanisms provides a basis for research into gender-specific responses to therapeutic interventions.

Gender-specific differences in therapeutic response to antidepressants

The most frequently prescribed antidepressants for individuals suffering from mild to moderate major depressive disorder (MDD) include selective serotonin reuptake inhibitors (SSRIs) (67). Besides, other classes of medications, such as serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants, are also considered to be of paramount importance in treating depression (68).

Despite the high prevalence of MDD and decades of therapeutic use, there is still no clear evidence on whether there are differences in the effectiveness of different classes of antidepressants depending on the gender (69). Studies have shown that there are indeed differences in the effectiveness of antidepressants, due to differences in drug selection, dosage, regimen, adherence and other factors, such as: percentage of adipose tissue and weight distribution, activity and expression levels of metabolic enzymes in the liver, hormonal fluctuations and changes in their concentrations during puberty, menstruation and menopause, gastric motility and secretion, plasma volume, interaction between estrogen and serotonin in the brain, etc. (68).

When examining the gender-specific efficacy of different types of antidepressants, literature data indicates that treatment with imipramine produced a better therapeutic response in men than in women (70), while various studies reveal that women respond better to SSRI (71-73). Notably, several studies which employed the Hamilton Depression Rating Scale (HAM-D) as the primary assessment tool indicative of SSRIs treatment efficacy demonstrated that the improvement was approximately 26% greater in women than in men (71, 72, 74). Younger women diagnosed with depression and receiving the SSRI fluvoxamine showed a significantly greater therapeutic response in comparison to men and women over 44 years of age (72). Furthermore, in a study that involved 138 patients, Vermeiden et al. (2010) reported gender-specific therapeutic effects depending on the antidepressant: men were more responsive to imipramine than premenopausal women, whereas women responded better to fluvoxamine than men (75). On the other hand, a study focusing on atypical depression provided conflicting findings: while MAOIs showed greater efficacy compared to TCAs in women, the opposite effect was observed in men (76). Importantly, a recent retrospective study revealed sex differences in clinical response to augmentation strategies, including antidepressants, mood stabilizers and/or antipsychotics, in patients suffering from treatment-resistant depression (TRD). Namely, it was observed that female patients diagnosed with TRD showed significantly greater improvement in sleep disturbances, anxiety and psychomotor retardation in comparison to male patients, following treatment with the respective pharmacological combinations (77).

However, in numerous studies no gender differences were observed in terms of antidepressant efficacy. In this context, a SNRI venlafaxine and SSRIs produced similar remission rates in men and women (78-80). In a large retrospective study that included depressive patients subjected to treatment with TCAs, MAOIs or SSRIs, the authors found no differences in therapeutic response between females and males (81). Similarly, Hildebrandt et al. (2003) reported that treatment with clomipramine, citalopram, paroxetine or moclobemide produced similar responses in women and men suffering from MDD. Importantly, a comprehensive meta-analysis involving 30 randomized, placebo-controlled studies on imipramine or amitriptyline also showed no sex-specific effects of TCAs in depressed patients (82-85). In addition, a meta-analysis performed by Kornstein et al. (2010) combined nine clinical trials which included adult patients with MDD (1108 men and 1805 women) who received desvenlafaxine or placebo for 8 weeks. The authors concluded that this SNRI led to significant remission of depressive symptoms, with similar responses observed in both sexes. In 2014, the same group of authors conducted another analysis of a double-blind clinical trial in which individuals diagnosed with recurrent MDD (670 women and 377 men) were subjected to 10 weeks of treatment with venlafaxine or fluoxetine. Similarly, no gender-specific differences in remission rates were detected following antidepressant treatment (79, 80).

The observed discrepancies in the literature data could be partially attributed to differences in social and demographic backgrounds, differences in the selected antidepressant drugs, as well as the dose, regimen and duration of antidepressant

treatment (69). A review investigating sexual dimorphism in antidepressant drug response emphasizes that there is currently no clear consensus on whether differences in symptom remission between male and female patients actually exist (68). Moreover, this review highlights the importance of different methodological approaches in the original clinical trials and the occurrence of several subtypes of depression with distinct features (68). Another important reason for these conflicting findings could be the age difference, particularly in women, as ovarian hormone synthesis and release significantly change with age and during menopause, thus exerting a substantial influence on the metabolism and antidepressant treatment response (86). In studies involving postmenopausal women suffering from MDD, the addition of estrogen to SSRI treatment resulted in greater improvement in depressive symptoms compared to SSRI alone (87). Besides, progesterone is known to reduce gastric motility, which may alter the pharmacokinetics of frequently prescribed antidepressants (88).

Premenopausal women with MDD generally show a better therapeutic response to antidepressants, particularly SSRIs, compared to postmenopausal women, which may be partly related to elevated plasma concentrations of follicle-stimulating hormone (FSH) in younger women (89). Interestingly, it was also demonstrated that reduced concentrations of luteinizing hormone (LH) in postmenopausal women may be directly related to a better response to antidepressants, as serotonin concentrations are thought to demonstrate an inverse correlation with LH levels (90, 91). Namely, reduced LH levels could possibly indicate higher basal levels of serotonin in these patients. On the other hand, a direct association was shown between reduced LH levels and increased activity of the HPA axis as one of the key features of MDD, further revealing the complex nature of the phenomena and the heterogeneity of depression (90, 91).

The phase of the menstrual cycle can also affect the therapeutic response to antidepressants in women. Hormonal fluctuations during the menstrual cycle influence gastric motility and volume of the extracellular fluid, resulting in changes in plasma drug concentrations in young female MDD patients (88). Importantly, women have a greater percentage of adipose tissue in comparison to men (92). Psychotropic drugs need to cross the blood-brain barrier, and they are mainly developed and synthesized as highly lipophilic substances. In this context, it is thought that lipophilic antidepressants display prominent sex-specific differences in volume of distribution, rate of redistribution and clearance (92). Furthermore, differences in hepatic blood flow, cytochrome P450 expression and enzymatic activity may also contribute to variations in metabolism and/or clearance of antidepressants between females and males, which inevitably leads to differences in plasma drug concentrations and therapeutic response (93, 94). All things considered, novel, large-scale and multicentre clinical studies are urgently needed to elucidate and further explore metabolic signatures and the epigenetic and genetic landscape potentially associated with sex-specific differences in antidepressant treatment response.

Conclusion

The described sex-specific differences in response to antidepressant treatment are most likely due to various biological factors that influence drug pharmacokinetics, including metabolism, distribution and elimination. Nevertheless, the conflicting findings highlight the complexity and variability of gender-specific responses, so that exact clinical implications remain uncertain.

Understanding gender dimorphism in the efficacy of depression treatments is a necessary step towards improving clinical outcomes and implementing personalized therapeutic approaches. Recognizing the complex interactions between biological, pharmacological, and sociocultural factors that determine sex differences in the treatment of depression is fundamental to treatment innovation. Research focused on endophenotypes and epigenetic mechanisms offers the opportunity to discover new biomarkers and molecular targets that may lead to personalized approaches in depression treatment. The use of genetic and hormonal testing and consideration of psychosocial aspects in clinical decision-making could significantly improve treatment strategies and patient adherence. Along with the abovementioned, separate approaches tailored to men and women that address gender-specific vulnerabilities could also provide great benefits in developing targeted interventions that meet the individual needs of patients with depression.

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Declaration of Competing Interests

The authors declare that they have no conflicts of interest to disclose, including financial, personal or other relationships.

Author contributions

JN: conceptualization, investigation, data curation, writing – original draft; **DS:** conceptualization, investigation, data curation, writing – original draft& editing; **JP:** investigation, data curation, writing – editing; **AI:** investigation, data curation; **MI** investigation, data curation; **GNS:** investigation, data curation; **BP:** conceptualization, investigation, supervision, project administration; **VP:** conceptualization, investigation, supervision, project administration, funding acquisition, writing – original draft& editing. All authors have read and approved the final version of the manuscript.

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Polne razlike u terapijskom odgovoru na antidepresive: biološka osnova i kliničke implikacije

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Kratak sadržaj

Depresija predstavlja ozbiljan zdravstveni problem na globalnom nivou koji pogađa milione ljudi i ograničava ih u obavljanju dnevnih poslovnih i privatnih obaveza. Istraživanja ukazuju na značajnu ulogu polnog dimorfizma u patogenezi i terapiji depresivnih poremećaja. Naime, pokazano je da između muškaraca i žena postoje značajne razlike u prevalenci, simptomatologiji i terapijskom odgovoru prilikom tretmana različitim grupama antidepresiva. Žene češće oboljevaju od depresivnih poremećaja, što se može pripisati hormonalnim uticajima i specifičnim mehanizmima suočavanja sa psihosocijalnim i drugim oblicima stresa. S druge strane, kod muškaraca je depresivna simptomatologija okarakterisana eksternalizovanim ponašanjem i višim stopama samoubistava u odnosu na žensku populaciju. Neurobiološke studije ukazuju na postojanje jasnih razlika u strukturi i funkciji određenih moždanih regija koje su specifične za pol. Takođe, između muškaraca i žena postoji razlika u aktivnosti neurotransmiterskih sistema, što može ispoljiti uticaj na efikasnost lečenja i dovesti do varijabilnosti u odgovoru na terapiju u zavisnosti od pola. Uz farmakoterapiju koja je osnova terapije depresivnih poremećaja, poslednjih godina se akcenat stavlja na personalizovan pristup u lečenju, koji integriše psihoterapijske modalitete poput kognitivno-bihejvioralne terapije i meditacije. Međutim, prisustvo razlika u ishodima lečenja u zavisnosti od pola naglašava potrebu za novim kliničkim strategijama. U prikazanom preglednom radu razmatrani su dostupni literaturni podaci u cilju isticanja važnosti personalizovanog pristupa u tretmanu depresivnih poremećaja kako bi klinički ishodi lečenja bili optimalni.

Ključne reči: depresija, polni dimorfizam, polne razlike, antidepresivi