Anxiety disorders in women: does gender matter to treatment?

Transtornos de ansiedade em mulheres: gênero influencia o tratamento?

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Abstract

Women have a substantially higher risk of developing lifetime anxiety disorders compared with men. In addition, research evidence has generally observed an increased symptom severity, chronic course, and functional impairment in women with anxiety disorders in comparison to men. However, the reasons for the increased risk in developing an anxiety disorder in women are still unknown and have yet to be adequately investigated. Evidence from various studies has suggested that genetic factors and female reproductive hormones may play important roles in the expression of these gender differences. The significant differences in onset and course of illness observed in men and women diagnosed with anxiety disorders warrants investigations into the need of differential treatment; however, evidence of gender differences in treatment response to different anxiety disorders are varying and remain largely inconclusive. This article reviews the prevalence, epidemiology, and phenomenology of the major anxiety disorders in women, as well as the implications of such differences for treatment.

Keywords: Anxiety disorders/epidemiology; Anxiety disorders/genetics; Anxiety disorders/drug therapy; Antidepressive agents/ therapeutic use; Depressive disorder; Disease susceptibility; Gender Identity Women's health

Resumo

Mulheres apresentam um risco significativamente maior comparado com o dos homens para o desenvolvimento de transtornos de ansiedade ao longo da vida. Além disso, diversos estudos sugerem maior gravidade de sintomas, maior cronicidade e maior prejuízo funcional dos transtornos de ansiedade entre as mulheres. Apesar disso, os motivos que levam a este aumento de risco no sexo feminino são ainda desconhecidos e precisam ser adequadamente investigados. Vários estudos apresentam evidências de que, entre as prováveis causas dessa diferença entre os sexos, estão os fatores genéticos e a influência exercida pelos hormônios sexuais femininos. As diferenças de gênero encontradas nos transtornos de ansiedade em relação ao início e à evolução da doença indicam que é necessário investigar a necessidade de tratamentos diferenciados para homens e mulheres. Entretanto, as evidências de que as diferenças de gênero modifiquem a resposta ao tratamento dos transtornos ansiosos ainda são inconsistentes e amplamente inconclusivas. Este artigo procura rever a literatura existente a respeito da prevalência, epidemiologia e fenomenologia dos transtornos ansiosos entre as mulheres e as implicações destas peculiaridades para a melhor eficácia no seu tratamento.

Descritores: Transtornos da ansiedade/epidemiologia; Transtornos da ansiedade/genética; Transtornos da ansiedade/quimioterapia; Transtorno depressivo; Antidepressivos/uso terapêutico; Identidade de gênero; Saúde da mulher

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Introduction

Anxiety disorders are the most prevalent psychiatric disorders as a group, with an estimated lifetime prevalence of 28.8%and an estimated 12-month prevalence of 18.1% in the general population.[1-2] The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) classifies generalized anxiety disorder (GAD), panic disorder, agoraphobia, social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), specific phobias, and post-traumatic stress disorder (PTSD) as anxiety disorders.[3] Only recently have researchers turned their attention to the occurrence of anxiety disorders in women. Data from recent U.S. community surveys has revealed that women have a significantly higher risk than men of developing an anxiety disorder during their lifetime. Thus, it is critical to investigate the characteristics and potential causes of anxiety disorders in this specific population.

According to U.S. community surveys, women are significantly more likely than men to develop panic disorder (7.7% vs. 2.9%), GAD (6.6% vs. 3.6%), or PTSD (12.5% vs. 6.2%) during their lifetime.[4] Though less pronounced, these surveys also suggest a gender difference in the risk for developing lifetime OCD (3.1% of women vs. 2.0% of men) and SAD (15.5% of women vs. 11.1% of men). The cause of the increased risk in women for developing a lifetime anxiety disorder is not understood. Relatively few studies thus far have investigated whether the characteristics of women with anxiety disorders differ from those in men with the same disorders.

Analyses of female twin registries have provided valuable insight as to the factors involved in the development of anxiety disorders in women. Data from these surveys suggest the potential role of genetic versus environmental factors in the development of anxiety disorders.[5-7] Data also suggests the potential role of female reproductive hormones and related cycles in the development, course, and outcome of anxiety disorders in women.[8-9] Published data has shown a gender difference in the absorption, bioavailability, and distribution of psychotropic medication, which will play an important role in the future of possible treatment methods for women with anxiety disorders.[10-11] Finally, recent findings from imaging studies have suggested that a more active and larger anterior cingulate cortex may exist among women with a distinct fear response and high harm avoidance scores as compared to men with similar characteristics.[12-13] Although such findings have not been studied in any specific anxiety disorder and are only preliminary results, they could explain, in part, the greater susceptibility of women to anxiety disorders. This article attempts to review these issues using the available evidence regarding anxiety disorders in women.

Generalized anxiety disorder (GAD)

The National Comorbidity Survey (NCS) estimates a 5.7% lifetime prevalence rate for GAD.[2] This survey demonstrated that women are approximately twice as likely to have GAD as their male counterparts, with total lifetime prevalence rates of 6.6% and 3.6%, respectively.[14] The prevalence rate increased to 10.3% for women aged ⩾ 45 years, but was unchanged for men aged ⩾ 45 years (3.6%).

GAD is characterized by excessive anxiety and worry occurring more days than not for at least 6 months, about a number of events or activities.[3] The symptomatology associated with this disorder includes restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and/or sleep disturbance. Women with GAD appear to have several distinguishing clinical features from men with GAD. Women diagnosed with GAD tend to have an earlier age of onset than men with GAD.[15] Women with GAD appear to be more likely to have comorbid psychiatric disorders, in particular depressive disorders, than men with GAD.[16] Data collected from three large household samples suggest that women with GAD may be more likely to develop comorbid dysthymia.[17] Comorbid GAD, as opposed to pure GAD, is associated with increased disability and dysfunction, and has a worse prognosis and impairment.[18] Analysis of population-based twin database has suggested that in women, GAD has a close genetic relationship to major depressive disorder (MDD).[5] It is hypothesized that relatively distinct environmental factors affect the expression of a GAD phenotype or an MDD phenotype. Thus, women with GAD may be more likely to develop comorbid conditions, such as depression, therefore affecting the course and severity of their illness.[7]

Evidence from various studies has revealed that women with GAD often report premenstrual worsening in GAD symptoms.[19] A study by McLeod et al compared women with GAD, GAD and premenstrual syndrome (PMS), and women controls and reported that women with GAD and PMS had more symptoms than the controls during both phases of the menstrual cycle and during the premenstrual period.[20] They did not report a significant change in symptom severity during the menstrual cycle in the women with GAD alone.

Evidence from some studies has suggested that women with GAD are more likely than men with GAD to seek professional treatment for their disorder, especially if they are also diagnosed with one or more comorbid disorder.[21] Medications reported to be effective in the treatment of GAD include buspirone, benzodiazepines, venlafaxine, and the selective serotonin reuptake inhibitors (SSRIs) antidepressants.[22] Due to the high rates of comorbid depressive disorders, effective antidepressant medications are generally recommended as first-line treatment for GAD. However, evidence has shown that women with GAD are more likely than men to be prescribed benzodiazepines.[23] These findings have several important implications. First, women with GAD have been found to have an increased risk for depressive disorders than men, and this should be taken into account when determining their treatment options. Second, animal models of anxiety have been examined for response to anxiolytic medication, and data from these studies has suggested response to these medications, in particular benzodiazepine, may be significantly influenced by gender as well as the phase of the estrous cycle.[24] Very few studies have specifically examined the relationship between gender and treatment response in GAD, but the limited data available has suggested that there is no significant gender differences for response to antidepressant treatment in GAD.[25] This includes results from a recent study conducted by Steiner et al, which found neither significant interaction between

gender and treatment group nor a significant difference between the average change from baseline in HAM-A and CGI-I scores for men compared with women.[15]

Panic disorder

The NCS estimates a 4.7% lifetime prevalence rate for panic disorder in the United States.[2] Of the U.S. population surveyed suffering from panic disorder, approximately 70% of those diagnosed were women compared with 30% men.[26] Analysis from this data revealed that among female respondents age 15-24 years, the rate of panic disorder was 2.5%, compared with 1.3% for their male counterparts.[27] The gender difference was found to increase by age. Among female respondents age 35-44 years, the rate of panic disorder was 2.1% compared with 0.6% for same-age male respondents. Additionally, data from international studies has shown evidence that women have significantly higher prevalence rates for panic disorder on a worldwide basis.[19]

Panic disorder is characterized by recurrent unexpected panic attacks followed by at least one month of persistent concern about having additional attacks, worry about the implications of the attack or its consequences, and/or significant change in behavior related to the attacks.[3] Panic disorder may or may not be accompanied by agoraphobia. Yonkers and colleagues found that women were more likely than men to have concurrent agoraphobia (85% versus 75%).[28] They also reported that 55% of the patients in their sample with panic disorder were women, and 71% of those with panic disorder with agoraphobia were women. Several studies have also indicated that in addition to an increased lifetime prevalence rate of panic disorder in women, panic attacks also occur more frequently in women than in men.[29]

Data from various epidemiological samples has yielded conflicting results concerning the average age of onset of panic disorder in women and men.[30-31] Using data collected from the NCS, Wittchen and Essau reported that panic disorder was most prevalent in women between the ages of 25 and 34 years, whereas it was found to be most prevalent in men between the ages of 30 and 44 years.[30] However, Clayton et al reported in a more recent study that women with panic disorder have a relatively later age of onset than men with panic disorder.[32] They also found that postmenopausal women with panic disorder may have significantly lower ($p \leqslant 0.05$) anticipatory anxiety, panic attack frequency, and panic severity than younger women and non-significantly lower avoidance and anxiety sensitivity.

According to data from the NCS, there appears to be a gender difference in the symptomatology of the disorder. Specifically, a significantly greater proportion of female subjects experience respiration-related symptoms (difficulty breathing, feeling faint, and feeling smothered) during panic attacks.[26] In a study of patients suffering from panic disorder with agoraphobia, women reported more severe agoraphobic avoidance when facing situations or places alone, more catastrophic thoughts, more body sensations, and higher scores on the Fear Survey Schedule.[33] In an Edmonton, Canada, population survey, Dick et al reported that women who meet criteria for panic disorder subsequently suffer from more individual panic symptoms and significantly greater levels of phobic avoidance compared with men with panic disorder.[31] They also reported that women with panic disorder are significantly more reliant on family members when entering fearful situations and have significantly more reports of panic attacks being triggered by leaving home alone or by using public transportation.

Examining symptom recurrence, Yonkers and colleagues reported that at 3 years the cumulative probability of 1 week of symptom recurrence for patients with panic disorder with or without agoraphobia was 0.73 for women and 0.43 for men; however, this difference was not statistically significant.[28] When they applied a more rigorous definition of symptom recurrence, and when severity of panic symptoms and history of alcohol abuse or dependence were included in the statistical model, women were still more likely to re-experience panic or agoraphobic symptoms.

Several studies have indicated that women with panic disorder have an elevated lifetime risk compared with men for developing comorbid psychiatric disorders in general and certain comorbid disorders in particular.[19,28] Women with panic disorder tend to have higher rates of comorbid agoraphobia, depression, GAD, simple phobia, and/or somatization disorder compared with men with panic disorder.[28,34] Turgeon et al have reported that women with panic disorder and agoraphobia more often have a comorbid social phobia or post-traumatic stress disorder compared with men with panic disorder and agoraphobia.[33] Finally, evidence has shown that women with panic disorder are more likely to have comorbid alcohol abuse or dependence compared with women without panic disorder, suggesting a possible genetic link between panic disorder and alcohol abuse in women.[35-36] The higher prevalence of comorbid disorders in women with panic disorder may result in a more chronic and severe course of the illness than in men.

Gender differences in the etiology and pathophysiology of panic disorder have yet to be extensively investigated.[19] Data from the female twin studies conducted by Kendler et al has suggested that genetic or familial factors play a modest role in panic disorder.[6,37] Results from a community survey conducted by Stein and colleagues have suggested the association between childhood sexual abuse and the development of panic disorder in adult women.[38]

Several studies have indicated the considerable impact of the female reproductive hormone cycles on the clinical course of panic disorder in women. Retrospective studies have reported that women with panic disorder experience an increase in their anxiety and panic symptoms during the midluteal or premenstrual phase of the menstrual cycle,[39-40] perhaps due to the dramatic decline in estrogen and progesterone levels that occur during this time. However, these results conflict with those from prospective studies, which have failed to discover a link between menstrual cycle phase and severity of anxiety or panic symptoms in women with panic disorder.[41-42] Other studies have shown evidence that sudden estrogen withdrawal, such as occurs in perimenopausal women and women who take birth control pills or receive Norplan implants, may be associated with the emergence of panic disorder in women.[43-44] More recently, a study demonstrated that panic disorder may arise and worsen with menopause, in correlation

with greater severity of the climacteric syndrome in its physical and psychological symptoms.[45] Northcott and Stein have reported the highly variable influence of pregnancy on the course of panic disorder in women, estimating that of women with pre-existing panic disorder, 40-45% experience no change in their symptoms, 30-35% experience an improvement in their symptoms, and 20-30% experience a worsening of their symptoms during the course of pregnancy.[46] Finally, Sholomskas and colleagues have suggested the association between the postpartum period of pregnancy and in an increased risk for the onset of panic disorder in women, estimating that 11-29% of women with panic disorder report onset of the illness during the postpartum period.[47]

At this time, little information is available concerning the potential impact of gender on treatment response in panic disorder. Selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), tricyclic (TCA) antidepressants, and high-potency benzodiazepine medications have all demonstrated efficacy in the treatment of panic disorder.[48] Results from a few preliminary studies have suggested a potential gender difference in treatment response in panic disorder.[32,49] However, further studies focusing on treatment response in women with panic disorder are necessary.

Social anxiety disorder (SAD)

The NCS estimates a 12.1% lifetime prevalence rate for SAD.[2] The NCS has demonstrated that SAD is the most common anxiety disorder and the third most common psychiatric disorder, exceeded in lifetime prevalence only by major depression (16.6%) and alcohol abuse (13.2%). An earlier version of the NCS has demonstrated that women are approximately 1.5 times more likely than men to have social anxiety, with total lifetime prevalence rates of 15.5% and 11.1%, respectively.[4]

SAD, also known as social phobia, is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others.[1] Two main subtypes of the disorder have been classified, generalized and nongeneralized. The generalized subtype of SAD includes individuals with a broad range of social fears, whereas the nongeneralized subtype primarily involves anxiety that is limited to specific situations.

A study by Turk et al examined specific gender differences among patients with SADs. They reported that women exhibited more severe social fears than men as indexed by several assessment instruments.[50] Additionally, gender differences were evident regarding severity of fear in specific situations. Women reported significantly greater fear than men while talking to authority, acting/performing/giving a talk in front of an audience, working while being observed, entering a room when others are already seated, being the center of attention, speaking up at a meeting, expressing disagreement or disapproval to people they do not know very well, giving a report to a group, and giving a party. Men reported significantly more fear than women regarding urinating in public bathrooms and returning goods to a store. This study did not show evidence of gender differences in the prevalence of the generalized versus nongeneralized type of SAD, the occurrence of comorbid disorders, or in the clinical course of the disease.

Other studies, however, have shown gender differences in the epidemiology of SAD. Yonkers et al examined data from the Harvard/Brown Anxiety Research Program, reporting that on average, women with SAD had more comorbid psychiatric illnesses than men (2.4 comorbid psychiatric illnesses compared with 1.9; $t = 2.05$, $df = 161$, $p < 0.4$).[51] They found that the illnesses most likely to co-occur among women were panic disorder with agoraphobia (50 % of women and 28% of men; $p < 0.005$) and simple phobia (24% of women and 9% of men; $p < 0.017$). They also found that a slightly larger proportion of women than men had generalized social phobia (56% vs. 47%) and that a smaller proportion of women had the specific form of social phobia (44% vs. 53%); however, neither difference was statistically significant. These gender differences may explain the more chronic course, with increased symptom severity and greater functional impairment, observed in women with SAD.

There is relatively little data available regarding gender differences in treatment response in SAD. While women have been shown to have a higher lifetime risk for developing SAD, evidence from two studies have indicated that men are more likely to seek treatment for the disorder.[52] In a placebo-controlled trial investigating the efficacy of paroxetine in the treatment of SAD, Stein et al reported that there was no evidence of a gender difference in response rates between men and women with SAD receiving treatment with paroxetine.[53] The same group also published recently a double-blind placebo controlled study of escitalopram for SAD, where the treatment effects of escitalopram were independent of gender.[54] Regardless, the impact of female reproductive hormones on the course and severity of social anxiety has yet to be thoroughly investigated.

Obsessive-compulsive disorder (OCD)

The NCS estimates a 1.6% lifetime prevalence rate for obsessive-compulsive disorder (OCD).[2] However results from the Epidemiologic Catchment Area (ECA) study and the Cross-National OCD Collaborative Group Study estimate a relatively higher lifetime prevalence rate for OCD (2%-3%) in the United States.[55] These same surveys indicate that women are 1.5 times more likely than men to develop OCD during their lifetime. However, the age of onset appears to differ between men and women, as data has suggested that prepubertal boys are 3 times more likely to be diagnosed with OCD as prepubertal girls.[56] The mean age of onset of OCD in men and women is 20 years and 25 years, respectively.[57] After menarche the prevalence rate of females with OCD greatly increases, suggesting the potential role of female reproductive hormones in the development of the disorder.

OCD is characterized by obsession as defined by recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress, as well as by repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.[3] There is some evidence that the course of OCD may be more episodic and

less severe in women than in men, and that women with OCD may have a more acute onset of OCD than men.[58]

Several studies have indicated that the pathophysiological mechanisms in OCD seem to differ by gender. Castle et al reported that females with OCD were more likely to be married and to have children than their male counterparts.[59] They also found that females were marginally more likely to have a past history of an eating disorder or depression, while males were more likely to have a history of anxious or meticulous personality traits. Lensi et al also found gender differences in the presentation of the illness.[60] They reported that women had higher rates of associated panic attacks after the onset of OCD and a higher frequency of aggressive obsessions at the onset of their illness. Valleni-Basile et al have reported that in adolescents with OCD, symptoms in females with OCD are characterized by compulsive rituals, whereas males are more likely to have obsessive thoughts.[61]

Based on data from clinical studies involving the serotonergic probes fenfluramine and clomipramine, there is some evidence of serotonergic mechanisms in OCD, especially in women.[62-63] This is further supported by findings that women with OCD appear to have a higher lifetime risk of comorbid disorders linked to serotonin dysregulation, including depression, panic disorder, PTSD, and eating disorders.[19] Some studies have also suggested the existence of potential gender differences in the genetic susceptibility for OCD.[64-66] In regards to treatment response, data from two OCD treatment trials with clomipramine and fluoxetine failed to demonstrate evidence of gender differences in medication response.[67]

Several reports provided evidence of the potential relationship between the menstrual cycle and increased OCD symptom severity in women.[68-70] In the largest of these studies, Williams and Koran reported that nearly half of their sample (42% of 57 women with OCD) experienced premenstrual worsening in their OCD symptoms.[70] They also reported their findings regarding the course of OCD during pregnancy, the postpartum period, and the premenstrual cycle, revealing that in their sample of women with preexisting OCD, 69% did not experience a significant change, 17% experienced a significant worsening, and 14% experienced improvement in their OCD symptoms during pregnancy. They also found pregnancy to be associated with the onset of OCD in 13% of the patients, and postpartum worsening of OCD symptoms occurred in 29% of the women with preexisting OCD.[70] A more recent study also obtained similar findings as in a substantial number of patients, the onset or worsening of OCD was related to reproductive cycle events, especially at menarche and postpartum.[71] These results provide strong evidence that the occurrence, severity, course, and outcome of OCD in women is substantially influenced by the female reproductive hormone cycles.

Post-traumatic stress disorder (PTSD)

Of the many individuals who are exposed to trauma, one in four will develop post-traumatic stress disorder (PTSD).[4] The NCS estimates a 6.8% lifetime prevalence rate for PTSD in the United States.[1] Data from such population surveys have suggested that women are twice as likely as men to develop lifetime PTSD (12.5% lifetime prevalence in women vs. 6.2% lifetime prevalence in men).[72]

PTSD is characterized by persistent re-experiencing of a traumatic memory, persistent avoidance of stimuli associated with the traumatic event, numbing of general responsiveness, and persistent symptoms of increased arousal.[4] Several studies have shown evidence towards a gender difference in the types of trauma that lead to the development of PTSD. Whereas the most common cause of PTSD in men is combat exposure, the most common causes of PTSD in women are sexual assault, sexual molestation, or childhood physical abuse.[72] Evidence has also shown the importance of "perceived threat" in the formation of PTSD in women, or the perception within the victim that the traumatic event is life-threatening or that escape is unlikely rather than more objective or realistic assessments of life-threatening events.[19]

Male military veterans are diagnosed with PTSD at a much greater rate than female military veterans; however, several studies have indicated that this data may be misleading. Pereira examined male and female veterans exposed to similar levels of combat-related stress and found that men and women were equally likely to have PTSD symptoms.[73] Kimberling et al examined PTSD in female Vietnam War-era veterans and found that there was a significant relationship between PTSD symptoms and reported health problems in the women with previous trauma exposure,[74] and it has been suggested that high rates of chronic medical illness may be one of the adverse consequences of failing to identify and diagnose PTSD in military veterans.[19] The results from these studies perhaps indicate that women in fact have a similar risk for PTSD as men after combat-related trauma exposure; they are simply less likely to receive a PTSD diagnosis than men.

Several studies have also indicated a gender difference in the symptomatology of PTSD. Fullerton et al examined the occurrence of PTSD in men and women after a serious motor vehicle accident, and found that women were nearly five times as likely to meet the overall avoidance/numbing criterion and almost four times as likely to meet the overall arousal criterion for PTSD.[75] They also found that dissociative symptoms at the time of the accident were associated with a significantly higher risk for acute PTSD in women than in men. Magdol et al found that women victimized by domestic violence are more likely to develop anxiety symptoms, whereas men are more likely to develop substance use disorders.[76] Additionally, women who suffer recurrent or chronic sexual abuse may be more likely to have anxiety and phobic symptoms and to develop an anxiety disorder.[77]

Evidence from several studies has suggested that women with PTSD may have an increased risk for certain pregnancy complications. Seng et al discovered that women with PTSD have significantly higher odds ratios for ectopic pregnancy, spontaneous abortion, hyperemesis, preterm contractions, and excessive fetal growth compared with a comparison group of women.[78] At this time, however, there is little systematic information available regarding the potential impact of the reproductive cycle in women with pre-existing PTSD.

There is some evidence of a gender difference in treatment response to PTSD. Sertraline and fluoxetine have been found

to be more effective in treating the symptoms of avoidance/numbing and hyperarousal compared with re-experiencing symptoms.[79-80] Since there is evidence that women are more likely to experience avoidance/numbing and hyperarousal symptoms than men,[81] this may account for the gender effect observed in these multicenter trials. A multicenter trial investigating paroxetine in the treatment of PTSD yielded no evidence of gender differences or differential response of PTSD symptom clusters.[82]

Discussion

Data from various epidemiological samples have suggested that women are approximately twice as likely to meet lifetime criteria for panic disorder, GAD, and PTSD, and approximately 1.5 times more likely to meet lifetime criteria for OCD and SAD. Evidence in the literature has also shown that in addition to a higher prevalence of anxiety disorders in women, gender differences also exist in the clinical presentation and features of such disorders and in the prevalence of comorbid psychiatric conditions. Women with anxiety disorders report higher symptom severity and tend to be more likely to have one or more comorbid conditions compared with men. These differences may serve to complicate the disorders and can result in a more chronic course of illness and greater functional impairment in women. Evidence from various studies has suggested that genetic factors and female reproductive hormones may play important roles in the expression of these gender differences. Notwithstanding such gender differences, there is paucity of data regarding treatment response among women with anxiety disorders as compared with men, and the limited evidence available is varying and largely inconclusive at this time. Future genetic and imaging studies may help elucidate the neurobiological basis for the observed epidemiology and clinical presentation differences between women and men. Further studies investigating gender differences in treatment response to various pharmacological and psychosocial interventions used to treat anxiety among women are warranted.

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