



Review Article

Sex Differences in Anxiety Disorders: A Review

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Abstract

Women have consistently shown to be more likely than men to meet criteria for the diagnosis of an anxiety disorder during their lifetime. Prior research has demonstrated that presence of an anxiety disorder confers significant risk for the subsequent development of other psychiatric disorders including another anxiety disorder and major depression. Studies investigating this increased vulnerability to and burden of illness in women have implicated the role of female reproductive hormones and related cycles, physiologic differences leading to differences in symptomatology and metabolism and response to psychotropic medications. There is also evidence of differences in brain structures responsible for anxiety and panic related circuitry. In spite of these noteworthy differences, there are limited systematic reports describing the effects of biological sex on the development, course, comorbidity, and response to treatment of anxiety disorders. In this article, we provide a review of existing literature describing the unique characteristics of primary anxiety disorders in women, including Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and Panic Disorder (PD). We have incorporated the changes in nosology made in the DSM-5 and have reviewed available data on the potential impact of sex on the epidemiology, phenomenology, course, and treatment response of these anxiety disorders. We also provide a brief overview of the potential genetic and neurobiological factors, discuss biological sex differences in medication metabolism and the potential relevance of these differences in the pharmacologic management of women with anxiety disorders.

Introduction

Anxiety disorders are one of the most commonly occurring psychiatric illnesses, with nearly one-fourth of adults in the United States meeting criteria during their lifetime [1]. Results from the National

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Comorbidity Survey (NCS) conducted in 1990-1992 [2] and the National Institute of Mental Health (NIMH) Collaborative Psychiatric Epidemiology Studies (CPES) from 2002-2003 [3] revealed that women were more likely than men to develop an anxiety disorder, with 30.5-33% women being diagnosed vs 19-22% men. Lifetime prevalence rates in the NCS for individual anxiety disorders like Panic Disorder (PD), Agoraphobia (AG), Specific Phobia (SP), and Social Anxiety Disorder (SAD), were also greater in women.

The emergence of anxiety disorders is typically during childhood, adolescence or early adulthood, with a peak occurring in middle age and a subsequent decline in older individuals. Although these disorders are more prevalent in women throughout their lifespan, there is a notable narrowing in the differences among the two sexes after the age of 65. It is hypothesized that several factors can contribute to these findings including cumulative effects of anxiety-related mortality, difficulty differentiating between cognitive impairment and an anxiety disorder, and the impact of female reproductive hormone cycle cessation [4].

Anxiety disorders can lead to the development of several adverse consequences including reduced educational and occupational opportunities, greater functional impairment and overall increase in morbidity and mortality rates as compared to those without an anxiety disorder [5-8]. They are associated with increased utilization of emergency medical and mental health services and have also been linked to elevated rates of teenage pregnancy and parenthood [9,10]. Additionally, anxiety disorders are also associated with several comorbid psychiatric diagnoses, especially mood disorders like Major Depressive Disorder (MDD) [6,11,12]. Sex differences in these comorbidities are also notable with MDD and Bulimia Nervosa (BN) being more prevalent in women and substance use disorder, Attention Deficit Disorder with Hyperactivity (ADHD), or intermittent explosive disorder being more likely to be present in men [3]. The same study also reported that women are more likely than men to have a comorbid anxiety disorder (44.8% versus 34.2%).

Various factors including genetic, neurodevelopmental, environmental, and neurobiological, are hypothesized to be responsible for the sex differences reported in anxiety disorders. There are significant brain structural and functional differences between men and women in areas relevant to anxiety, including the prefrontal cortex, hippocampus, and the extended amygdala complex [13]. Female reproductive hormones, especially estrogen and progesterone, may also have a critical role in the neurobiology of anxiety disorders [14-17]. They have been hypothesized to provide critical modulating effects within the CNS that may influence the presentation, course, and treatment response of anxiety disorders in women [18-21]. Periodic fluctuations in estrogen and progesterone levels throughout the lifespan of women (i.e., during menarche, during the menstrual cycle, pregnancy, and the post-partum period, and in peri-menopause and post-menopausal periods), can also precipitate responses in the Hypothalamic-Pituitary-Adrenal (HPA) axis [22]. These wide fluctuations in gonadal steroid and glucocorticoid responsive brain systems likely contribute to the changes in anxiety symptom severity observed during the

various reproductive phases in women [23,24]. Altemus, 2006 [23] has postulated that the increased prevalence of anxiety disorders in females may be a recent development. That is, in evolutionary terms, the ability of gonadal hormones to suppress the HPA axis and the catecholamine stress response system during pregnancy and lactation may have protected females against the development of anxiety disorders. However, now that modern females spend much less of the time between puberty and menopause being either pregnant or lactating, the critical defense strategy provided by gonadal hormones is lost. In males, the primary reproductive hormone, testosterone, appears to have anxiolytic effects by reducing responsiveness to stress and suppressing HPA axis activity [25].

The gut microbiota has been linked to a variety of stress-related conditions, including anxiety disorders [26] and this has largely been investigated in studies with Germ-Free (GF) animals or correlative analysis in patient populations. Male GF animals were found to have elevated levels of serotonin metabolites, as compared to conventionally raised controls. Concentrations of tryptophan, the precursor of serotonin, were noted to be increased in the plasma of male GF animals in the same report, thereby suggesting a humoral route through which the microbiota can influence CNS serotonergic neurotransmission [27]. Davis et al., [28] found that male socially isolated mice whose diets were supplemented with a fatty acid displayed reduced anxiety behaviors compared to controls, while no differences were seen with female mice. Additionally, introduction of the fatty acid induced sex-specific interactions on the gut microbiome with the fatty acid producing a significant effect on the microbial profiles in males but not in females.

The response to treatment of anxiety disorders can also differ in the two sexes. The sex-related phenotypic differences in the hepatic P450 system, which critical to the metabolism of the most commonly prescribed medications for anxiety disorders including antidepressants and benzodiazepines, can result in significant variances in psychotropic plasma concentrations between men and women given the same dose of medication. Additionally, bioavailability and absorption of psychotropic medications is influenced by the female hormone progesterone due to its association with reduced gastric acid production. Despite these findings that suggest that these pharmacokinetic differences may impact the absorption and relative amount of medication present, there is limited data concerning potential sex differences in anxiety disorder treatment response [29-31].

Keeping the above critical issues in mind, the authors report the impact of sex on the epidemiology, phenomenology, course, and treatment response of anxiety disorders including Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and Panic disorder (PD) based on review of current and recent literature. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [32] no longer classifies Obsessive Compulsive Disorder (OCD) and Posttraumatic Stress Disorder (PTSD) as Anxiety Disorders, and hence these disorders have not been included in this review article.

Generalized Anxiety Disorder (GAD)

Overview and epidemiology

Data from large-scale epidemiologic studies such as the NCS and NCS Replication (NCS-R) studies estimated the lifetime prevalence of GAD between 5% and 6% [2,33]. More recent studies such as the

NCS-R and CPES describe a notable sex difference in prevalence rates, with women consistently reported to have an increased rate of GAD in comparison to men [3,34,35]. In primary care settings, GAD is reportedly the second most common psychiatric disorder after depression [36]. Patients with GAD exhibit deficits in social and role functioning, general health, and bodily pain thereby leading to more disability days and a greater number of physician visits than patients without GAD [37,38].

Around 90% of individuals with GAD have comorbid psychiatric conditions. Mood disorders were the most common lifetime comorbid disorder in those meeting criteria for GAD, with unipolar depression (67%) reportedly four times more likely to occur than bipolar disorder (17%) in the NCS study [9]. GAD is also frequently comorbid with other anxiety disorders such as PD and SAD [39].

Despite the availability of efficacious treatments, research suggests that most patients with GAD remain untreated. In a survey conducted in 127 patients meeting criteria for GAD, the average interval between the onset of GAD and the initiation of the first adequate medication trial was 81.6 months [40]. Antidepressants in the class of Selective Serotonin Reuptake Inhibitors (SSRIs; such as Paroxetine, Citalopram, Sertraline, Fluoxetine, and Escitalopram) are considered to be first-line in the treatment of GAD. Norepinephrine and Serotonin-Selective Reuptake Inhibitor (NSRI) antidepressants (Duloxetine and Venlafaxine) are also considered to be highly effective pharmacotherapy for GAD. If effective, antidepressant treatment for GAD should be continued for at least 12 months [41]. Studies have also investigated the role of Pregabalin, an inhibitory neurotransmitter that acts by its ability to bind to the $\alpha 2\text{-}\delta$ subunit of voltage-gated calcium channels in the central nervous system [42]. Daily doses of 150 mg, 300 mg and 600 mg have been found to be effective in randomized control trials for short-term treatment of GAD [42-44]. Cognitive Behavioral Therapy (CBT), has demonstrated significant value and similar treatment effect sizes as those associated with effective pharmacotherapeutic agents (SSRI and NSRI) in GAD [45,46]. Treatment response rates in GAD range between 47% and 75% for CBT, whereas response rates with pharmacotherapy range between 44% and 81% [47]. Alternatives to SSRI and SNRI antidepressants for treatment-resistant or treatment-intolerant GAD patients include tricyclic antidepressants, Buspirone, second-generation antipsychotics (Quetiapine), and Valproate [48]. There do not appear to be improved outcomes with combination (medication plus CBT) treatment in GAD in comparison to pharmacotherapy or CBT alone [49,50].

Sex differences in GAD

Women are 2- to 3-times more likely than men to meet lifetime criteria for GAD [3,34,35]. Differences are also noted in the symptoms exhibited in the two sexes, with women endorsing more somatic complaints, fatigue, and muscle tension than men [51]. McLean et al., [3] theorized that the increased somatic complaints may reflect the influence of social and sex-specific factors, as women are more prone to internalizing disorders compared to men. Females may also be more likely than males to have negative affect and neuroticism, and such traits have also been implicated as risk factors in the development of anxiety, in general, as well as GAD, in particular [52].

While epidemiological studies have not detected a difference in age of onset, course or chronicity of GAD between the two sexes [3,33,34,51], reports from clinical samples have found an earlier onset

of GAD in females than in males [36]. Women in the prospective HARP study were noted to have lower rates of remission than men and remission also occurred later [36]. Rodrigues et al., [53] conducted in a sample of primary care patients found similar results in that men were significantly more likely than women to achieve a partial recovery from GAD.

The 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study, a large cross-sectional survey of over 43,000 participants in the U.S., revealed that men meeting criteria for GAD had significantly higher rates of comorbid alcohol and drug use disorders, nicotine dependence, and antisocial personality disorder than women with GAD. Women meeting GAD criteria in comparison to men had significantly higher rates of comorbid mood disorders (except bipolar disorder) and anxiety disorders (except SAD). Males also reported greater use of alcohol and drugs to help relieve GAD symptoms, whereas women with GAD were more likely to report a family history of depression and greater levels of disability. Although relatively few sought treatment in the same report, men were even less likely than women to pursue treatment for GAD [51].

Comorbidity with depression has been associated with increased functional impairment and a greater risk of suicide. Given that women are more likely to have GAD with comorbid depression, this likely contributes to the finding that women are more likely than men to have a more chronic course of GAD and greater symptom severity. Data from bivariate female twin pairs with GAD suggests that genetic factors accounted for approximately 30% of the risk of GAD development, with environmental factors explaining the remainder of the variance [54,55].

There are mixed results concerning the potential impact of the female reproductive cycle on the course of GAD. One report found that over half (52%) of women with GAD reported premenstrual worsening of GAD symptoms [56]. However, a prospective study conducted in females with GAD failed to detect any difference in GAD symptom severity across the menstrual cycle [57]. The risk of GAD appears to be increased during pregnancy; with prevalence rates during pregnancy (8.5%-10.8%) consistently exceeding those reported for non-pregnant women in the general population [58-60]. Symptoms of GAD were more noted to be more pronounced during the first and third trimesters in two studies that examined the course of GAD across pregnancy [61,62]. A previous history of GAD, a lower education level and support, and a history of childhood abuse, are factors associated with development of GAD in pregnancy [59].

The prevalence of GAD in the post-partum period ranges from 4.4%-10.8% [60,63,64]. Women diagnosed with GAD 10 weeks after childbirth were more likely to report sexual fear, avoidance, and body image self-consciousness compared with post-partum women without GAD [65] and are more likely to have comorbid MDD [66]. The presence of GAD in pregnancy has also been associated with significantly lower levels of fetal brain-derived neurotrophic factor; this finding has led to concerns about a potential negative impact on fetal neurodevelopment [67].

There is limited data available concerning the potential impact of sex on treatment response in GAD. There was no evidence of sex differences in GAD treatment response in a double-blind, placebo-controlled trial of sertraline [31], but another study revealed that females with GAD were less likely to respond to SSRIs than males [68].

Although benzodiazepines are not considered first-line pharmacotherapy in anxiety disorders, results from a survey in the Netherlands completed by more than 60,000 patients seen in general practice settings revealed that women in comparison to men were twice as likely to receive a first prescription for benzodiazepines and were also found to have a significantly higher rate of repeat benzodiazepine prescriptions. These findings indicated less stringent prescribing guidelines for benzodiazepines in women and a lack of re-evaluation by the prescriber of the initial prescription during repeat prescriptions, thereby accounting for the sex differences in benzodiazepine use [69].

Social Anxiety Disorder (SAD)

Overview and epidemiology

Data from the NCS and other large epidemiological studies (NCS-R, ESEMeD) have reported the lifetime prevalence of SAD to be in excess of 13%, with females are more likely than males to develop SAD, with odds ratios between 1.2 and 1.5 [2,8,70]. The most commonly feared situation reported in SAD is public-speaking anxiety, while meeting strangers, eating in public, cashing checks in public, and using public restrooms are some other frequently described scenarios [71].

The onset of SAD is usually in adolescence or early adulthood, often before the age of 18; onset after the age of 25 is uncommon, and it usually follows a chronic and unremitting clinical course [36]. Onset of symptoms at a younger age and comorbid alcohol use can lead to more chronic clinical course [36]. Functional consequences associated with SAD include lower education attainment, increased workplace impairment, and an increased reliance on welfare rather than wages [72]. This study also reports that these effects were independent of the effects of depression.

The DSM-IV classified SAD into a generalized and a non-generalized subtype. Epidemiological surveys reported that two-thirds of those meeting criteria for SAD were in the generalized subtype and one third was in the non-generalized subtype [2,73]. In the DSM-5 however, the subtypes of SAD were replaced by a specifier for a performance-only type of SAD. This change was predicated on the assumption that SAD likely exists on a continuum of symptom severity ranging from a few to many feared social situations and related avoidance behaviors; therefore, the distinction between generalized versus non-generalized SAD subtypes likely represented symptom severity rather than distinct groups defined by shared genetic, neurobiological, or other features. The performance-only specifier is limited to performance fears that are typically most impairing in professional settings or in roles that require regular public speaking, and may also manifest in work, school, or academic settings in which regular public presentations are required. Individuals with the performance-only type of SAD do not fear or avoid non-performance social situations. Using the DSM-5 criteria, the National Survey of Mental Health and Well-Being (NSMHWB) conducted in over 8800 adults in Australia reported an overall lifetime prevalence rate of 8.4% for SAD, with 0.3% meeting criteria for the performance-only specifier [74]. This study also found higher prevalence rates in females, frequent (70%) comorbid conditions, and relatively low rates of treatment-seeking (20%) in those with SAD. There is limited research that utilizes DSM-5 criteria and hence in this review, we describe data derived from studies using DSM-IV criteria, including the generalized and non-generalized subtypes of SAD.

SAD is frequently complicated by comorbid psychiatric disorders, with most data estimating lifetime risk at 60-80% [2,6,75]. The NCS also reported an increased risk of developing MDD (three-fold increase), dysthymia (2.7-fold increase), and bipolar disorder (six-fold increase), and an association with more severe and chronic mood disorders [76]. SAD with comorbid disorders is associated with greater clinical severity and increased treatment rates [75] and an increased risk of suicide attempts [8,77]. Despite the potential for grave outcomes, SAD continues to be underdiagnosed and inadequately treated [73,78]. In a large study of primary care patients, 5% met criteria for SAD, but less than half (46%) were recognized as having a psychiatric disorder if they were not also depressed. Although 76% of the depressed patients with SAD were identified as having a psychiatric illness, only 11% were correctly identified as having an anxiety disorder [79]. Data from the NESARC study indicates an average delay of 16 years between the onset of SAD and initiation of first treatment [80].

A recent neuroimaging study conducted on SAD patients focused on serotonin synthesis rates in neural pathways implicated in fear response within the amygdala. Not only were enhanced rates of amygdala serotonin synthesis identified in the patients with SAD in comparison to controls, but symptom improvement was associated with a reduction in amygdala serotonin synthesis rates [81]. These results suggest that the neurobiological abnormalities underlying SAD may include an enhanced serotonergic tone within the amygdala that exerts an anxiogenic influence and that effective pharmacotherapy in SAD may be mediated at least in part by decreasing serotonin formation in the amygdala. Functional Magnetic Resonance Imaging (fMRI) studies conducted in participants with SAD while performing a task designed to assess anticipation of social reward and punishment revealed that controls (n=20) had significantly greater striatal activation for reward versus punishment trials compared to the SAD group (n=20) [82]. The authors postulate that the usual motivational preference for social reward rather than punishment may be attenuated in individuals with SAD.

SSRI antidepressants and venlafaxine are considered first-line pharmacotherapy in SAD. A meta-analysis of seven trials that compared SSRIs with placebo in a total of 896 patients with SAD found that SSRIs resulted in greater symptom reduction compared with placebo and had a moderate effect size [83]. Although less well studied than the SSRIs, the SNRI venlafaxine extended release appears to be equally effective for SAD on the basis of a comparable effect size compared with various SSRIs in meta-analysis [84]. Cognitive-behavioral therapy is also a well-established first line therapy in SAD that may also be a helpful adjunct in non-responders to pharmacological treatments [85]. A recent meta-analysis of 36 randomized-controlled trials revealed medium to large positive effects for Cognitive-Behavioral Group Therapies (CBGT) in comparison wait list-controlled trials in alleviating symptoms of SAD. No significant differences were detected in the direct comparisons of group or individual psychotherapy or pharmacotherapy for SAD in the same report [86].

Sex differences in SAD

Women are reported to have a slightly higher risk of developing SAD in comparison to men. Wittchen et al., 1999 [73] described a community sample of young adults, in which women meeting criteria for SAD were more likely to endorse feared situations related

to eating or drinking in public, writing while someone was watching, talking to others, and participating in social events than men with SAD. In a clinical sample, women endorsed a greater number of feared social situations and more intense fear in comparison to males [87]. The only two feared situations reported more in men than women were urinating in public bathrooms and returning goods to a store. Sex differences are also reported in comorbid conditions with SAD; SAD females may be significantly more likely to have comorbid psychiatric disorders, especially mood disorders, than SAD males. However, shared genetic vulnerability may partly contribute to this association between SAD and mood disorders in women [88].

Of all the anxiety disorders, SAD may be the one most shaped by social influences. Females with SAD may be particularly prone to develop comorbid internalizing disorders such as mood disorders, whereas men with SAD may be more likely to develop more social or external ways of coping such as alcohol or drug use which can lead to substance use disorders [89]. Data from the NESARC survey conducted in the U.S. provided additional support for this idea. Women meeting criteria for SAD not only reported a greater number of social fears, but they also were more likely to have comorbid internalizing disorders and were more likely to seek treatment with medication than men meeting criteria for SAD. In contrast, men meeting criteria for SAD were more likely to report dating-related fears, have comorbid externalizing disorders, and to also use alcohol and illicit drugs for symptom relief [90]. Although data from an epidemiologic catchment area health survey (n=2434) found that being male, younger, feeling stigmatized, and scoring higher on impulsiveness were predictors of substance dependence, it also revealed that females meeting criteria for substance dependence were more likely to have comorbid SAD than males with substance dependence [91]. In adolescent girls with SAD, however, drug use was noted to be less likely in a community sample [92].

Childhood trauma has been linked to an increased risk of SAD. In the NCS study, childhood sexual assaults by a relative and chronic exposure to verbal outbursts between parents were linked to the onset of SAD in females but not males. In fact, there was no link between childhood adverse experiences and onset of SAD in males as part of the NCS [93]. Findings from the NCS-R survey completed in adolescent girls (n=2486) suggested a unique interplay between early exposure to trauma, onset of menarche, and subsequent risk of SAD. That is, trauma during puberty in comparison to other developmental periods conferred a significantly greater risk of an anxiety disorder diagnosis (primarily SAD) within 2 years after menarche. The authors suggest that menarche may amplify social sensitivity in females, making them particularly vulnerable to the effect of trauma during puberty [94].

There is emerging data concerning the prevalence, onset, course, and risk factors for SAD during pregnancy and post-partum. Goodman et al., 2014 [95] report prevalence of SAD in pregnancy ranging from 2-4% in populations in different countries. Three studies specifically compared rates of SAD in pregnant versus non-pregnant female controls. Adewuya and colleagues [58] found that the prevalence of SAD in pregnant Nigerian women (6.4%) was significantly higher than that found in non-pregnant females (2.8%). In contrast, rates of SAD were similar in pregnant (3%) compared to non-pregnant females (2.8%) in studies conducted in the United States [51] and Turkey (3.2% during pregnancy versus 2.8% in non-pregnant controls;)

[67]. The presence of SAD during pregnancy may also be associated with an increased risk for post-partum depression [96].

There may be some differences in brain structure between men and women with SAD. In a 3-dimensional structural magnetic resonance imaging study, SAD patients (n=24) had significantly reduced amygdala (13%) and hippocampal (8%) size in comparison to control subjects (n=24). Further analysis revealed that the reduction in amygdala size was only statistically significant in the men with SAD. Smaller right-sided hippocampal volumes in the SAD patients were also significantly related to greater severity of SAD [97].

Panic Disorder (PD)

Overview and epidemiology

Panic Disorder (PD) is a condition wherein people experience multiple, recurrent Panic Attacks (PAs), with at least some of these attacks occurring at unexpected times. PAs have an acute onset, peak within minutes, and must fulfill a set number of defined somatic and psychological criteria. In addition to panic attacks, behavioral requirements, such as avoidance or anticipatory anxiety, are also necessary to meet criteria for PD [32]. Prior to the DSM-5, Agoraphobia (AG) was classified as a subordinate condition within the diagnosis of PD [98], but the DSM-5 categorized PD and AG as separate disorders, each with its own distinct diagnostic criteria.

Bandelow and Michaelis, [99] described the variability noted in the prevalence of PD. Data from the ECA (N=24,371) and the NCS-R (N=9,282) studies completed in the United States revealed lifetime prevalence rates for PD of 1.6% and 5.2%, respectively. The NCS-A survey revealed a lifetime PD prevalence of 2.3% for those aged 13-17 years. Results from the European Study of the Epidemiology of Mental Disorders (ESEMED, N=21,425) estimated a 1.6% lifetime prevalence rate for PD.

The presence of PAs alone increases the odds of developing phobias, GAD, OCD, or PTSD with the estimated risk ranging from three to sixteen-fold in the literature. PAs have also been associated with an increased risk for mood disorders, in general, and MDD, in particular, as well as personality disorders and substance use disorders [100]. PD is associated with a chronic course, high rates of comorbid disorders and significant disability. PD is highly comorbid with MDD and the presence of MDD in PD conveys an increased risk for substance use disorders as well as for additional anxiety disorders [101]. PD with AG was associated with more severe PD, elevated suicide risk, and higher levels of anxiety sensitivity, neuroticism, and trait anxiety than PD without AG. Moreover, comorbid hypomania and SAD were also more likely to occur in PD with AG than in PD without AG [102].

Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants are considered first-line pharmacotherapy for PD. Randomized trials have shown that Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, and Escitalopram to be effective for PD compared to placebo. Trials have shown SSRIs to reduce the frequency of panic attacks, severity of anticipatory anxiety, and degree of phobic avoidance. A systematic review and meta-analysis of 12 trials of acute treatment for PD found the SSRIs to be efficacious compared to placebo, with a medium effect size [103]. Venlafaxine Extended Release (ER) has also been found in randomized trials to be an efficacious treatment for PD [104,105]. Numerous randomized trials have found Alprazolam, Clonazepam, Lorazepam, and Diazepam to be efficacious for each of

the three components of PD (attack frequency, anticipatory anxiety, and phobic avoidance [106]. However, given the potential for abuse of benzodiazepines and the lack of efficacy in the treatment of comorbid mood disorders in PD, their use in the treatment is limited.

Sex differences in panic disorder

Women are more likely to endorse more individual panic-related symptoms than men and also to display more avoidance symptoms [24]. Differences in specific symptoms reported to occur during panic attacks in men and women may be accounted for by the differences in their pathophysiology. Sex differences in sensitivity to CO₂ and in the threshold for panic attacks during hypoxic and hypercapnic states likely contribute to these findings [107]. Men with PD display greater general fatigue symptoms and have reduced activity than control subjects, whereas women with PD score higher than controls for physical fatigue, but do not differ from them in areas of general fatigue and activity levels [108].

Results from a study utilizing the National Institute of Mental Health Panic Questionnaire (NIMH PQ) also revealed differences in the characteristics of AG in female and male patients with Panic Disorder with Agoraphobia (PDA) [109]. Women are more likely to avoid buses, being in unfamiliar situations alone, and more likely to stay at home to avoid agoraphobic situations than men. Men with AG, on the other hand, have greater avoidance for staying at home alone. Females are more likely to more impaired and appear more dependent than men in terms of requiring companions to move outside of the home. Females also display more severe agoraphobic avoidance, whereas males with PDA are more likely to worry about their physical health and also about the potential for serious somatic consequences from having panic attacks [110]. No sex differences are detected in the age of onset, illness duration, panic attack severity or frequency, or severity of anxiety, depression or general psychiatric symptoms in PDA [109,110].

Susceptibility to comorbid conditions including AG, MDD, GAD, and somatoform disorders is greater in women [111]. Patients with AG have more severe symptoms of panic disorder and a higher level of neuroticism, sensitivity to anxiety, and trait anxiety. Women are also more likely than men to have PDA and have a greater prevalence of comorbidities, including hypomanic episodes, social phobia, and a higher risk of suicide and relapse [102,112].

Clayton et al., [113] described sex differences in the treatment response to Sertraline. Clinical Global Impression-Improvement scale (CGI-I) scores and frequency of panic attacks showed a greater improvement in women as compared to men, but there were no significant between-sex differences are seen in study completion rates, or in adverse event profiles. Women with more severe symptoms noted on the Panic and Agoraphobia Scale (PAS) showed a greater response to treatment with Gabapentin than men in another study [114].

A major metabolite of progesterone is the steroid allopregnanolone, which is a potent positive allosteric modulator of GABA_A receptors, a subset of receptors which make up the predominant inhibitory neurotransmitter system in the brain [115]. Animal models studying the panic circuitry involving GABA receptors-rich Periaqueductal Gray (PAG) region of the brain have found that this circuitry is more excitable via decreased GABAergic inhibition in rats during the late diestrous phase, which is a state of low progesterone (and, thereby, a relative decrease in allopregnanolone). In contrast, for female pubertal

rats, the highest rates of anxiolytic and antidepressant behaviors as measured by behavioral paradigms occur in the proestrous phase of the estrous cycle, when allopregnanolone levels are at their peak [115]. Concurrent with the increase in rates of PD for women at puberty is a decrease in, or relative withdrawal of, allopregnanolone in the hippocampus [116]. A clear relationship between progesterone and panic symptomatology in humans has yet to be elucidated as multiple studies have not found an association between the two. An earlier study has documented premenstrual worsening of symptoms in 51% of participating women with AG [117], while another small study of women with PD reported that 79% retrospectively felt an increase in anxiety pre-menstrually, with 58% reporting increased frequency of panic attacks and 47% recalling more phobic avoidance [118].

In a systematic review of anxiety disorders during pregnancy, prevalence rates of PD were noted to vary widely, from 0.2 to 5.7%, based on 12 studies [95]. Rates of up to 0.9% for AG without history of panic were found, with rates up to 17.2% for AG of any type. This systematic review established a broad prevalence rate of 0 to 53.8% for the new onset of PD during pregnancy. The course of AG during pregnancy was also noted to be varying with four studies demonstrating an improvement in symptoms, four showing minimal change, and the one study reporting worsening of symptoms. In contrast to the course of PD during pregnancy, the postpartum period has traditionally been considered a time of increased risk of PD onset as well as PD exacerbation. In the reported largest sample (N=128) investigating the course of PD during postpartum, Bandelow and colleagues [119] demonstrated a small increase in panic symptomatology when compared to both the pregnancy and the non-pregnancy periods. There was also a large rise (a 132-fold increase) in the incidence rate of PD during the postpartum period. As might be expected, women with PD and AG were more symptomatic than women with PD without AG.

Conclusion

The above findings indicate that sex differences exist in the prevalence, clinical features, and comorbid conditions that may complicate anxiety disorders, including GAD, SAD and PD. The emerging picture is that these disorders are more common in women than men and also more likely to be chronic, complicated by comorbid psychiatric disorders, and associated with more functional impairment. Large-scale epidemiologic studies have concluded that women can have a 2 to 3 fold increase in the occurrence of GAD and PD and women are more likely than men to meet lifetime criteria for SAD with a greater number of social anxiety-related fears and greater overall symptom severity. Fluctuations in levels of female hormones progesterone and estrogen throughout the lifespan during the various phases of the menstrual cycle, can significantly influence the course and severity of anxiety disorders in females. Pregnancy has been associated with an increased risk for GAD, while varying results were found in women with PD and SAD. Women with pre-existing GAD and SAD appear to be at substantial risk for developing depression and additional anxiety disorders during the post-partum period and symptoms of PD are also known to be exacerbated during this time. Currently, consistent sex differences in treatment response to these disorders have not been reported. There is some preliminary evidence suggesting sex differences in brain structure i.e., in the prefrontal cortex, hippocampus, and the extended amygdala complex of the brain, the areas relevant for anxiety symptoms. Data also suggests that childhood stress or trauma may increase risk for the later emergence of SAD and GAD,

the timing of which may be particularly important in females. Further research is warranted that would focus on interventions and treatment of these debilitating anxiety disorders, keeping the above sex-related issues in mind in order to improve outcomes in women.

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