Gender Differences in the Epidemiology and Treatment of Anxiety Disorders

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Women are more likely than men to develop anxiety disorders. Yet, relatively few studies have investigated whether women with anxiety disorders have characteristics that are distinct from those of men with the same disorders. The cause of the enhanced vulnerability to anxiety for women remains largely undetermined. Recent data suggest that female reproductive hormones and related cycles may play an important role. In addition to etiologic functions, reproductive hormones may substantially influence the clinical course of preexisting anxiety conditions in women. Psychotropic medications are more likely to be prescribed to women, and gender differences have been identified in the pharmacokinetics of psychotropic medication. Yet, relatively few systematic data are available concerning the potential clinical relevance or possible treatment implications of gender differences in the treatment of women with anxiety disorders. This article reviews the unique characteristics of primary anxiety disorders in women, summarizes the neurobiological effects associated with estrogen and progesterone, discusses gender differences in medication metabolism and the potential relevance of these differences in the pharmacologic management of women with anxiety disorders, and reviews issues specific to women (e.g., hormone therapy, oral contraceptives, menstrual cycle, pregnancy, lactation) that may impact treatment with psychotropic medication.

(J Clin Psychiatry 1999;60[suppl 18]:4–15)

Anxiety disorders represent the most common psychiatric disorders in the United States, and epidemiologic surveys reveal that 1 of 4 individuals will experience an anxiety disorder during his or her lifetime.[1,2] Generalized anxiety disorder (GAD), panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder (OCD), simple phobia, and posttraumatic stress disorder (PTSD) are classified as anxiety disorders in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).[3] Data from U.S. community surveys confirm that women are twice as likely as men to develop panic disorder (7.7% vs. 2.9%), simple phobia (13.9% vs. 7.2%), or PTSD (11.3% vs. 6.0%) during their lifetime. Although there is less of a gender difference, lifetime prevalence estimates also suggest that women are at increased risk for OCD (3.1% vs. 2.0%) and social anxiety disorder (3.2% vs. 2.3%)[4–6] (Figure 1). Unfortunately, relatively few individuals who meet full diagnostic criteria for anxiety disorders receive psychiatric treatment.[1]

In a series of seminal reports, Kendler and associates[8–11] analyzed data obtained from a female twin registry to investigate the potential role of genetic versus environmental factors in the development of anxiety disorders. These studies provide intriguing evidence that vulnerability to anxiety disorders, at least in women, may be largely determined by genetic factors. However, susceptibility for developing an anxiety disorder is unlikely to arise from a single gene or the same genetic foundation. Instead, the characteristics of the individual anxiety disorders are sufficiently different from each other that at least 2 separate and distinct genetic determinants are likely to be involved in mediating the overall risk that any anxiety disorder will emerge. Data from the Kendler studies suggest that one genetic factor may markedly increase the risk of occurrence of phobias and panic disorder, whereas a different genetic factor may be responsible for the development of GAD and major depression.[8,9]

GENERALIZED ANXIETY DISORDER

Two large epidemiologic surveys conducted in the United States, the Epidemiologic Catchment Area (ECA) Study and the National Comorbidity Survey (NCS), esti-

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Presented at the symposium "New Treatments for Anxiety Disorders: Clinical Approaches for Successful Outcomes," which was held May 31, 1998, in Toronto, Ontario, Canada. This symposium was held in conjunction with the 151st annual meeting of the American Psychiatric Association and supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.

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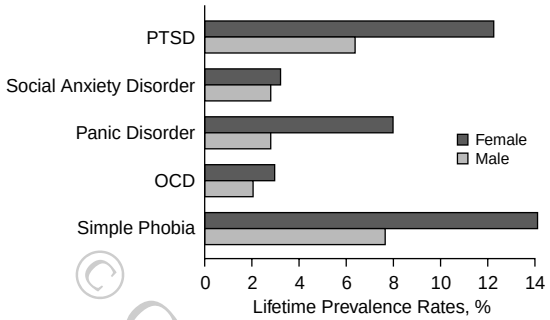
Figure 1. Lifetime Prevalence Rates for Anxiety Disorders[a]



[a]Data from references 4, 5, and 7.
Abbreviations: OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder.

mate a 5% to 6% lifetime prevalence rate for GAD. GAD develops twice as often in women compared with men.[1,12] GAD has a chronic course and is associated with increased utilization of medical and mental health services and increased consumption of psychotropic medication.[13]

Several clinical features appear to distinguish women from men with GAD. Dysthymia may be more likely to develop in women with GAD.[5] The presence of a comorbid diagnosis is associated with a worsened prognosis and reduced remission rates compared with those in patients with GAD alone.[14] Genetic factors, rather than environmental factors, may be particularly important in determining liability for developing GAD in women. Similar genetic factors appear to enhance vulnerability for developing major depressive disorder and GAD. It is hypothesized that specific and distinct environmental risk factors mediate expression of the specific phenotype (GAD versus major depressive disorder) if this genotype is present.[15] These results suggest that women with GAD are more likely to develop comorbid conditions and that the presence of such coexisting diagnoses may reduce the likelihood of remission.

PANIC DISORDER

The lifetime prevalence rate for panic disorder is between 1.5% and 2.0%.[16] Panic disorder, as well as panic attacks, is twice as frequent in women compared with men.[17–19] Panic disorder appears to have some distinct features in women. Women with panic disorder report more individual panic-related symptoms.[20,21] Women also have an elevated risk of developing agoraphobia and other avoidance behaviors as a complication of panic disorder.[17,19,22] Comorbid psychiatric disorders, such as GAD and simple phobia, also are more common in women with panic disorder.[19,23,24] Alcohol abuse is a complication of panic disorder, and women with panic disorder are particularly prone to developing dependence.[17,23] Because an elevated rate of alcohol dependence also has been reported in the relatives of women with panic disorder, a shared genetic diathesis between panic disorder and alcohol abuse may exist.[9,25,26]

Women with panic disorder also appear to be particularly vulnerable to somatization disorder as a comorbid condition.[19,23,27] In fact, some studies suggest that somatization disorder is 4 times more likely to occur in women with panic disorder.[25] Women with comorbid panic disorder and somatization disorder are more likely to have relatives with antisocial personality disorder.[25,26] These results suggest that women with panic disorder are particularly likely to have comorbid (i.e., complicated) panic disorder. Because complicated panic disorder is associated with a more severe, refractory clinical course,[19,23,27,28] this likelihood may have important implications. Greater risk for comorbid disorders may also contribute to the greater functional impairment and more severe clinical course reported in women with panic disorder in comparison with men with panic disorder.[19,23,24,28]

SOCIAL ANXIETY DISORDER

Although the ECA survey suggested that social anxiety disorder was relatively rare (3%),[29,30] subsequent studies reveal a much higher lifetime prevalence rate for social anxiety disorder (13%).[1,31,32] Most studies have reported that women have a 1.5-times greater lifetime prevalence rate for social anxiety disorder compared with men.[31,32] Two main subtypes of social anxiety disorder, generalized and nongeneralized, have been identified.[1,32,33] The generalized subtype of social anxiety disorder includes individuals with a broad range of social fears, including performance and interactional situations, whereas the nongeneralized subtype primarily involves anxiety that is limited to specific situations, such as public speaking.

Data are relatively limited concerning potential gender differences in social anxiety disorder. Women with social anxiety disorder may have an increased risk for developing agoraphobia.[20,21,33] Several studies conducted in women with social anxiety disorder have provided evidence that genetic factors are important in the development of the generalized subtype.[9,12,34,35] In fact, relatives of patients with generalized social anxiety disorder have an increased risk, perhaps as much as 10-fold, of developing the generalized subtype.[36] In contrast, relatives of patients with nongeneralized social anxiety disorder are not more likely to have social anxiety disorder.[36] Patients with social anxiety disorder complicated by panic disorder may represent a distinct subgroup in terms of genetic factors. They have an increased risk of having a relative with panic disorder, but not family members with social anxiety disorder.[26] These findings suggest that comorbid conditions may be more likely in women with social anxiety disorder and that generalized social anxiety disorder, at least in women, may be mediated by genetic factors.

OBSESSIVE-COMPULSIVE DISORDER

One of the most surprising findings from the ECA database was the relatively high lifetime prevalence rate for OCD (2%–3%) in the United States.[37] Data from the subsequent Cross National Collaborative Group study that included 6 international sites supported a similar lifetime prevalence rate for OCD.[38] Although most studies suggest that women are 1.5 times more likely than men to develop OCD during their lifetime, 3 times as many prepubertal boys as girls are diagnosed with OCD.[37,38]

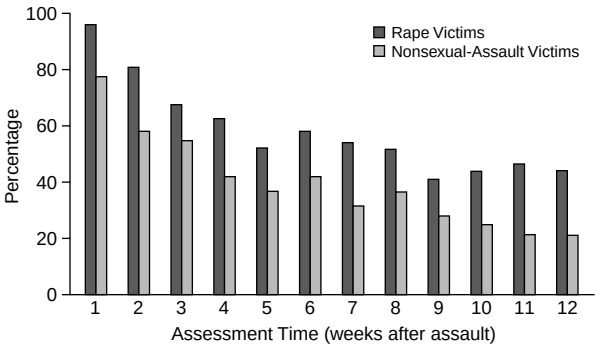
Several studies have systematically investigated the potential impact of gender on OCD. OCD has a later age at onset in women (mean age = 25 years) than in men (mean age = 20 years).[39,40] Boys are more likely than girls to develop OCD classified as early onset (before 10 years of age) or very early onset (before 6 years of age).[41,42] However, as noted, the incidence of OCD markedly increases in females and eventually surpasses that in males after puberty occurs.[37,38] Past history of an eating disorder, depression, panic attacks, aggressive obsessions, or cleaning rituals also are more commonly associated with females with OCD.[43–45] In contrast to the finding reported in GAD and social anxiety disorder, women with OCD may have an episodic and less severe clinical course than men.[40,46]

POSTTRAUMATIC STRESS DISORDER

Although many individuals are exposed to trauma, only 1 of 4 will develop PTSD.[4] The lifetime prevalence rate for PTSD is greater in women (12.5%) than men (6.2%).[1,15] The most common cause of PTSD in men is combat exposure. Women are most likely to develop PTSD as a consequence of a physical or sexual assault or threat, a life-threatening experience, or witnessing a life-threatening event. Several variables, besides gender, have been associated with an increased risk for developing PTSD. Victims of sexual, as opposed to nonsexual, assault are much more likely to develop PTSD.[47] Foa[47] evaluated women for 3 months after a criminal assault and compared the women who were victims of rape with those who were victims of a nonsexual crime. Rape victims were almost twice as likely to have PTSD (48%) compared with women victimized by nonsexual crime (25%) (Figure 2). Because women are more likely to be victimized by sexual assault, it is not surprising that the development of PTSD is higher in women.

In addition, gender differences have been identified in the acute, as well as delayed, response to severe trauma and abuse. Physical and psychological symptoms other than PTSD can arise after exposure to sexual or physical abuse. Women victimized by domestic violence are more likely to develop anxiety symptoms, whereas men may be at greater risk of developing substance use disorders in the context of ongoing abuse or violence.[48] An elevated rate of depression and increased risk for physical and psychological health problems also has been associated with ongoing domestic violence in women. Although physical symptoms and emotional distress are common sequelae of domestic violence, the presence of severe or life-threatening physical injuries does not reliably predict that psychiatric symptoms or PTSD will subsequently emerge.[49] Instead, "perceived threat," the victim's perception of danger during an assault, may be more important than objective or realistic assessments in the formation of PTSD.

Figure 2. Percentage of Victims With Diagnosis of Posttraumatic Stress Disorder: Rape Versus Nonsexual Assault, Assessed Weekly[a]



[a]Reprinted from reference 47, with permission.

Women who suffer recurrent or chronic sexual abuse may be more likely to have anxiety and phobic symptoms and to develop an anxiety disorder.[35] Childhood abuse, especially incest, is associated with particularly devastating consequences in women. An increased vulnerability for anxiety disorders, major depression, dissociation, somatization, eating disorders, drug and alcohol abuse, suicide attempts, and psychiatric hospitalizations have all been linked to sexual abuse during childhood.[50,51] Chronic pelvic pain and other diffuse somatic symptoms are reported at an elevated rate in women with a history of severe childhood sexual abuse.[52] Complications associated with childhood abuse are likely to persist into adulthood. Moreover, women who sustain childhood abuse endorse symptoms of physical and emotional distress and functional impairment that are similar in severity to those in women with ongoing, active abuse.[51]

Interestingly, most studies suggest that women are not at greater risk for traumatic exposure,[4,53–56] but are more likely to develop PTSD when exposed to trauma. For example, Breslau and colleagues[54] noted a similar rate of exposure to traumatic events between men and women in a sample of more than 1000 young adults, but substantially more of the women met PTSD criteria. Potentially confounding factors, such as increased prevalence of preexisting anxiety or major depressive disorders in women, were unable to explain the observed gender difference in PTSD. The age that the trauma occurred had an impact, and

women were particularly vulnerable to PTSD development, if the traumatic exposure occurred prior to age 15.[55]

The reason that women seem more vulnerable to PTSD and other anxiety disorders remains largely undetermined. However, considerable research recently has focused on the potential role of female gonadal hormones as possible mediators of increased susceptibility to the development and perpetuation of pathologic anxiety conditions.

HORMONAL FACTORS

Three primary neurotransmitter systems are traditionally considered to mediate anxiety: the locus ceruleus–norepinephrine system, the serotonin system, and the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex. However, female gonadal hormones, especially estrogen and progesterone, may have a substantial regulatory role in the function of these neurotransmitter systems in women[57] (Table 1).

Estrogen is neuroprotective with respect to neuronal degeneration, growth, and susceptibility to toxins,[58] and estrogen appears to facilitate serotonin function.[59,60] Trophic effects and ability to enhance serotonin neurotransmission have led to considerable speculation that estrogen may have mood-elevating properties.[60–62] In addition, stress response mediated by the locus ceruleus–norepinephrine system may be attenuated in the presence of estrogen.[63,64] Progesterone, in contrast, has been associated with biological effects that may oppose the actions of estrogen, and progesterone often is linked to dysphoric or mood-destabilizing effects.[59,65,66]

Because estrogen and progesterone have critical roles in the regulation of neurotransmitter systems considered to be important mediators of the anxiety response, they have been implicated in the higher vulnerability for anxiety disorders in women.[57,58,67] The marked cyclic fluctuations in estrogen and progesterone that occur as part of the reproductive cycle also may play an important role in enhancing susceptibility to developing anxiety, as well as substantially influencing clinical course and symptom severity, when anxiety disorders exist.[19,57,58,68–70]

Estrogen

Estrogen enhances neurotransmission by influencing the synthesis, receptor sensitivity, and metabolism of monoamines (e.g., norepinephrine, dopamine, serotonin).[69] Norepinephrine and dopamine activity also are enhanced by the ability of estrogen to decrease monoamine oxidase enzyme activity and alter tyrosine hydroxylase activity.[71] Estrogen also decreases the responsiveness of the α_2-adrenergic receptor, an autoreceptor, thereby facilitating norepinephrine neurotransmission.[59,60,71–73]

The effect of estrogen on norepinephrine via the α_2-adrenergic receptor may explain the difference in stress response between men and women. Men have greater release of norepinephrine than women after administration of a pharmacologic blocker of the α_2-adrenergic receptor. This finding is thought to represent the chronic attenuation of the α_2-receptor response in women by the presence of estrogen.[72,73] Results from positron emission tomography (PET) scan studies also support gender differences in response as measured by changes in brain metabolism when healthy volunteers receive agents that stimulate a stress response.[73] The exaggerated physiologic stress response reported in premenopausal and postmenopausal women, as well as the increased risk of cardiovascular disease after menopause, have been linked in part to loss of the ability of estrogen to suppress the stress response.[58,67,74]

Estrogen also impacts dopamine neurotransmission. Neuroleptic treatment is associated with similar effects on striatal dopamine-2 (D_2) receptors. Animal studies indicate that estrogen elicits a significant increase in the number of D_2 receptors within the striatum in the brain.[74] The synergistic action of estrogen on the D_2 receptors is thought to be the basis of the estrogen replacement therapy (ERT)–facilitated response reported in female schizophrenic patients treated with neuroleptic medication.[75] The impact of estrogen on dopamine also has been implicated in the pathophysiology of postpartum psychosis.[60,75–77] Because pregnancy is associated with a marked increase in endogenous estrogen production and concentration, subsequent changes in dopamine receptor number and responsiveness are likely to result. The precipitous drop in estrogen concentration that rapidly occurs within the postpartum period is hypothesized to trigger a supersensitivity reaction in the proliferated D_2 receptors. This enhanced responsivity within the dopamine system may contribute to an enhanced susceptibility for psychosis to occur.[78]

The effects of estrogen on serotonin may be most important in explaining the genetic difference in anxiety disorders. Estrogen enhances serotonin function through several actions. Serotonin transporter sites are increased and monoamine oxidase enzyme activity is decreased by the direct effects of estrogen.[57,58,60,71] Estrogen also impacts serotonin function by indirect actions. The initial pharmacologic action of many antidepressants is reuptake inhibition that generally occurs within a few days, but therapeutic effects are not apparent for several weeks. As a result, secondary pharmacologic actions, including down-regulation of serotonin receptors, are assumed to be critical to the onset of antidepressant action.[60,79]

Table 1. Biological Actions of Estrogen and Progesterone on Neurotransmitters, Synapse Function, and Mood[a]

Parameter	Estrogen	Progesterone
MAO activity	Decreases	Increases
Neurotransmission	Facilitates	Inhibits
Effect on mood	Enhances	Destabilizes
Effect on synapses	Trophic	Dismantles

[a]Data from reference 60. Abbreviation: MAO = monoamine oxidase.

Estrogen appears to have a critical role in the process of antidepressant-induced down-regulation of serotonin receptors. Data from animal studies suggest that the serotonin receptor adaptations necessary for the onset of antidepressant effects may be estrogen dependent in women.[62] Antidepressant action may be substantially impaired in the absence of estrogen. There is preliminary evidence that estrogen is an important facilitator of serotonin response in humans. Postmenopausal women without ERT have evidence of reduced serotonin response that can be effectively "normalized" with ERT.[80,81] Moreover, depressed elderly women were more likely to respond to SSRI antidepressant treatment when they were also receiving ERT.[81]

Progesterone

Less information is available concerning the actions of progesterone within the brain and central nervous system (CNS). Progesterone has been associated with well-documented dysphoric effects in women and also may be associated with some anxiolytic effects.[69,82] The anxiolytic action of progesterone has been attributed to its effects on the GABA-benzodiazepine receptor complex (GBRC).[83,84]

The GBRC refers to the structure composed of a GABA-A receptor and an adjoining chloride channel, with the benzodiazepine receptor site located in close proximity. The GABA-A receptor functions as a gatekeeper for the chloride channel. Binding of the neurotransmitter GABA to the GABA-A receptor site results in conductance of chloride through the channel. The channel remains closed to chloride conductance in the absence of GABA occupation of the GABA-A receptor. The benzodiazepine receptor acts as an allosteric modulator for GABA. Binding of a benzodiazepine to the receptor will not result in chloride conduction through the channel unless GABA also is present at the GABA-A receptor. Binding of a benzodiazepine in the presence of GABA will further enhance the ability of GABA-A to conduct chloride through the channel.[79] Results from recent studies suggest that progesterone also functions as an allosteric modulator of GABA, although its ability to facilitate chloride conduction is relatively weak in comparison to that of the benzodiazepines.[59,65] Because GABA is one of the major inhibitory neurotransmitters in the brain, neural suppression results when progesterone or a benzodiazepine promotes chloride conduction through the GBRC. The anxiolytic or sedating properties associated with the administration of benzodiazepines, and perhaps progesterone, in humans are considered to be mediated through the actions of GABA at the GBRC.

The action of progesterone at the GBRC may explain why women taking oral contraceptives have enhanced sedation, increased amnestic effects, and greater psychomotor impairment when administered benzodiazepine medication. The ability of progesterone to function as an allosteric modulator at the GBRC site is hypothesized to result in enhanced benzodiazepine receptor-binding sensitivity with a subsequent amplification of the pharmacologic effects of the benzodiazepine, which may have some clinically relevant implications.[83] Women coadministered oral contraceptives may require a reduction in benzodiazepine dose. In addition, the synergistic relationship between progesterone and benzodiazepines could be used for therapeutic benefit. Progesterone augmentation may represent a therapeutic option for women with anxiety disorders who fail, or only partially respond to, standard therapeutic regimens.

In contrast to estrogen, progesterone enhances monoamine enzyme activity.[71] Progesterone also plays a role in dismantling synapses constructed by estrogen at the beginning of the menstrual cycle. The role of progesterone in increasing monoamine catabolism, disrupting synapses, and suppressing neurotransmission is implicated in its mood-destabilizing effects. Most of the actions of progesterone result in antagonism and/or neutralization of the actions of estrogen.[59,65,82] As a result, the addition of progesterone to ERT may neutralize the mood-enhancing and stress-attenuating effects elicited by estrogen administration.[59,60,66,85] However, the complex metabolic pathway of progesterone results in the formation of multiple metabolites. Many of the metabolites of progesterone, such as pregnenolone and allopregnenolone, possess biological actions that are markedly different from those of the parent compound. Therefore, the net biological effects of progesterone are highly dependent on the prevailing metabolic pathway and the relative availability, and associated biological actions, of the various metabolites.[84,86]

IMPACT OF REPRODUCTIVE CYCLES

The female reproductive cycle is characterized by marked fluctuations in estrogen and progesterone concentrations throughout life. The cyclic changes in gonadal hormones are likely to have an important influence on the onset and course of anxiety disorders in women. Despite widespread clinical experience supporting this finding, there are few systematic data concerning the impact of reproductive cycles on anxiety disorders.

Menstrual Cycle and Menopause

Although menstrual-related emotional and somatic symptoms are quite frequent, premenstrual dysphoric disorder (PMDD) is estimated to occur in only 3% to 8% of women.[87,88] The presence of menstrual-related psychiatric symptoms does not necessarily support a diagnosis of PMDD. Because premenstrual exacerbations of depressive and anxiety disorders are not unusual, other Axis I disorders should be excluded before diagnosing PMDD. The presence of substantial menstrual-related psychiatric symptoms has been linked to the presence of an underly-

ing anxiety disorder rather than to a PMDD diagnosis. In addition, longitudinal studies suggest that the menstrual cycle can substantially influence the onset and course of anxiety disorders.[19,87]

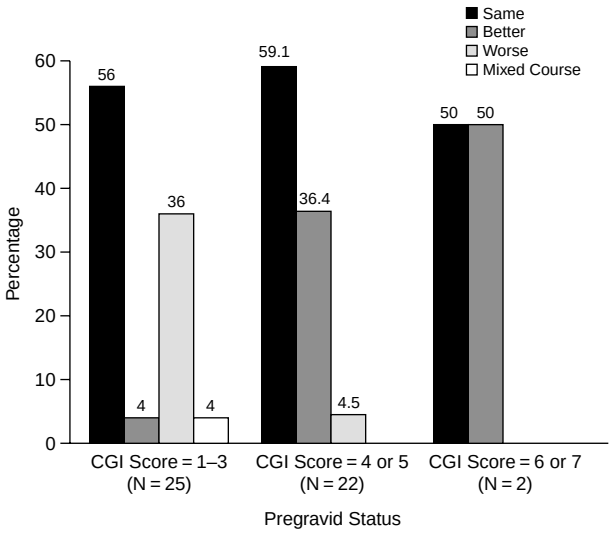
Premenstrual changes in the severity of symptoms of anxiety disorders are often clinically apparent. Premenstrual exacerbation in panic symptomatology has been reported.[6,68,89] However, some studies have failed to detect significant changes in panic symptoms during the menstrual cycle.[19,90] The premenstrual period has been more consistently reported to elicit exacerbations in OCD symptoms.[91,92] In the largest study to date, the impact of the menstrual cycle was retrospectively examined in 57 women with OCD. Nearly half (42%) of the women reported premenstrual worsening of OCD symptoms, and a substantial number (21%) also noted premenstrual dysphoria.[91] Menopause and estrogen-depletion states, as well as the use of oral contraceptives or hormone replacement therapy (HRT), have also been associated with the onset of, or substantial changes in, panic disorder and OCD.[19,57,67,93]

Pregnancy and the Postpartum Period

The impact of pregnancy and the postpartum period on anxiety disorders also has been the focus of several recent studies.[91,96–104] Although many women without preexisting psychiatric disturbance experience the emergence of psychological distress and somatic symptoms during pregnancy and the puerperium, it is important to recognize that the appearance of mood or anxiety symptoms does not necessarily herald the onset of psychiatric disturbance. Longitudinal studies of healthy female volunteers reveal that hypochondriacal concerns commonly emerge and increase in severity as pregnancy progresses. Anxiety complaints, such as fear of dying, are not infrequent during the third trimester. Development of such hypochondriacal preoccupations or anxiety symptoms rarely indicates the presence of psychiatric illness.[94] In contrast, persistent and sustained symptoms of dysphoria, worrying, somatic and psychic anxiety, insomnia, severe fatigue, anger, or irritability during pregnancy or the postpartum period have been associated with an enhanced risk for subsequently developing significant depression.[95]

Many of the data evaluating the impact of pregnancy and the postpartum period on anxiety disorders involve either panic disorder or OCD. The course of preexisting panic disorder is highly variable during pregnancy.[6,19,96] Women with preexisting panic disorder may remain well during pregnancy, even after discontinuing medication.[24,68,97] In the largest report, however, 80% of women with preexisting panic disorder (total N = 49) had little change in clinical status during pregnancy, but more severe panic occurred in 20% of the women (Figure 3). In contrast to earlier reports, pregnancy was not associated with successful discontinuation of antipanic medications in this large study.[89]

Figure 3. Relationship Between Course of Panic Disorder in Pregnant Women and Severity of Pregravid Panic[a]



[a]Data from reference 89. Clinical Global Impressions (CGI) scale: 1 = not at all ill, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = most ill.

The postpartum period traditionally has been considered a turbulent time for women with preexisting panic disorder. A significant portion (30%–60%) of women with panic disorder will experience an exacerbation or reemergence of panic during the postpartum period.[24,96,98,99] Fortunately, research has revealed that patients treated with antipanic medications during the third trimester experience significantly less postpartum worsening.[98] The postpartum period also may represent a time of enhanced vulnerability for the onset of panic disorder. In one study, 4 (29%) of 14 women reported onset of panic during the postpartum period.[24] Moreover, 11% of women met criteria for postpartum onset of panic in another report.[100]

In retrospective reports, substantial portions (13%–36%) of women with OCD have noted the onset of OCD during pregnancy or the postpartum period.[68,91] Several reports also suggest that women with preexisting OCD experience worsening symptoms during pregnancy.[68,101,102] However, recent large-scale investigations have not demonstrated that most women with OCD experience a substantial change in OCD symptoms during pregnancy. These studies support the finding that the postpartum period is often associated with an exacerbation in preexisting OCD. Results suggest that more than 30% of women with OCD experience postpartum worsening of symptoms.[68,91,103,104]

PSYCHOTROPIC MEDICATIONS: GENDER DIFFERENCES

Women are prescribed the majority of psychotropic medications, and more reversible drug-induced or

medication-induced psychiatric conditions are reported in women.[105] Despite these findings, little is known about the specific effects of gender on tolerability, safety, or efficacy of psychotropic medication. Hopefully, recent changes in the U.S. Food and Drug Administration (FDA) guidelines concerning inclusion of "women of childbearing potential" in clinical trials will help to provide further information about potential gender differences. Further information regarding the potential impact of reproductive cycles and coadministration of exogenous hormones on the efficacy and tolerability of psychotropic medication also is needed. Gender has a substantial impact on the pharmacokinetic profile of psychotropic medications.[65,70] Significant differences between men and women in the absorption, bioavailability, and distribution of psychotropic medication have been identified.

Absorption

Women have a reduced rate of gastric emptying[106,107] and more rapid small intestinal transit time,[108] which can result in reduced concentrations of ingested medication. However, gender differences also have been identified in other pharmacokinetic factors. Women have markedly reduced gastric acidity in comparison with men.[107,109] As a result, weak bases such as benzodiazepines and tricyclic antidepressants (TCAs) are absorbed more rapidly, resulting in higher plasma concentrations of these medications in women.[70,107] Some gastric enzymes also are less active in women. The consequence of reduced gastric enzyme activity is an elevation of plasma concentrations of the affected medications. Although significant gender differences have been identified in gastric acidity, motility, and enzyme activity, the clinical relevance of these findings remains undetermined.

Distribution

The distribution of medications is determined by several factors, including body size and fat composition, regional blood flow, and protein binding. Women tend to have lower body weight, reduced blood volume, and greater percentage of body fat compared with men.[110] Although lower body weight and blood volume contribute to higher plasma concentrations, higher percentage of body fat has the opposite effect and is associated with a greater volume of distribution and, at least initially, lower plasma medication concentrations.[107] Many psychotropic medications, such as benzodiazepines, are lipophilic and preferentially gravitate toward adipose tissue, where accumulation may prolong half-life.[111] Because body fat increases with age, lipophilic medications are particularly likely to deposit and accumulate in the fatty tissue of elderly patients.[112] Because elderly women have the greatest distribution of adipose tissue, they are the subgroup most prone to developing extensive accumulation of lipophilic medications. For example, bupropion has a substantially prolonged half-life due to its extensive volume of distribution when administered to elderly women.[113] These gender differences in pharmacokinetics can have important implications. Although elderly women are the largest consumers of psychotropic medication worldwide, relatively few studies have systematically investigated the potential role of gender or age and, perhaps most critically, the interaction of gender and age on the concentration of psychotropic medications.[114–118]

Protein Binding

Many medications are bound to plasma proteins, particularly α_1-acid glycoproteins and albumin. The total concentration of medication in the body is composed of bound and unbound (free) portions. Usually only the unbound portion of medication is active, capable of crossing the blood-brain barrier, and is associated with potential toxicity. Coadministration of 2 highly protein-bound medications can result in competitive displacement of one of the medications from the plasma proteins. The displaced medication will have a subsequent increase in unbound portion. New adverse effects or toxicity can appear as the unbound portion of the displaced medication increases. This can have important clinical consequences when medications with relatively narrow safety margins, such as warfarin, theophylline, or phenytoin, are displaced by tightly protein-bound medications.

Gender differences in protein-binding features have been identified. Women have lower plasma protein binding in comparison with men. Although protein-binding characteristics are fairly diverse for psychotropic medications, most anxiolytic medications are highly protein bound. Benzodiazepines (99%) and the antidepressants fluoxetine, sertraline, paroxetine, and nefazodone are more than 95% protein bound.[119] In contrast, TCAs (75%–95%) and fluvoxamine (77%) are moderately protein bound,[120,121] and the antidepressants citalopram (50%) and venlafaxine (38%) have relatively low protein binding.[122]

Protein-binding features can be important in situations in which the prescribed medication is studied under conditions in which it is highly protein bound but administered in situations in which it can become less protein bound. Benzodiazepines and TCAs are moderately to highly protein bound.[123,124] However, these agents are less protein bound in women than men. The relative increase in unbound concentration of TCAs may have clinical relevance for women because the TCAs have a relatively narrow therapeutic index. As a result, the protein-binding differences may contribute to a higher risk of adverse effects or toxicity in women compared with men who are prescribed a TCA at the same dose.

Protein-binding characteristics associated with the selective serotonin reuptake inhibitors (SSRIs) are particularly complex and difficult to assess in terms of clinical consequences. Most of the SSRIs, with the exception of

Table 2. Cytochrome P450 (CYP) Isoenzymes and Gender Differences[a]

P450 Isoenzyme	Female Gender	Older Age	Polymorphism
CYP3A3/4	Increased activity	Decreased activity	No
CYP1A1/2	Reduced activity in pregnancy and when taking birth control pills	No effect	No
CYP2C19	Increased activity	No effect	Yes

[a]Data from references 70, 119, and 125–134.

fluvoxamine and citalopram, are highly bound to plasma proteins. However, the strength of the attachment between the SSRI and the plasma proteins is relatively weak and primarily involves α_1-acid glycoproteins.[125] Therefore, coadministration of other highly protein-bound medications, such as warfarin or anticonvulsants, probably results in displacement of the SSRIs, rather than the other medication, from plasma proteins. Because SSRIs have a wide margin of safety, substantial elevations in unbound plasma concentrations of SSRIs are unlikely to have clinical relevance in terms of toxicity.

Metabolism

The liver metabolizes most psychotropic medications, including benzodiazepine and antidepressant medications. Several different systems are responsible for the metabolism of medications within the liver. Nonsynthetic, oxidative reactions, such as hydroxylation, are more sensitive to gender differences than are synthetic reactions, such as glucuronidation.[124] Both hydroxylation and glucuronidation reactions are slower in women than in men, and the lower metabolic rate results in lower clearance and higher plasma concentrations of medications metabolized by these pathways.[107,126] Women also have lower renal clearance rates compared with men, presumably due to lower glomerular filtration rates.[107] Because most psychotropic medications are renally excreted, metabolism and elimination of psychotropic medication also may be slower in women, resulting in slower elimination of psychotropic medications.

Cytochrome P450 System

A substantial portion of hepatic metabolism of psychotropic medication is mediated by the cytochrome P450 (CYP) enzyme system, which is composed of more than 30 separate isoenzymes.[119,125] The isoenzymes CYP2D6, CYP3A4, CYP1A1/2, and CYP2C19 are responsible for the metabolism of most psychotropic medications, as well as many routine prescription medications, such as β-blockers, opiate analgesics, anticonvulsants, antihistamines, calcium channel blockers, steroid medications, and macrolide antibiotics (Table 2).

The CYP2D6 isoenzyme is responsible for metabolism of multiple medications. Inhibiting the CYP2D6 isoenzyme can substantially increase plasma concentrations of medications that are metabolized by this enzyme. This mechanism is implicated in the toxic reactions noted when SSRIs, such as fluoxetine, are combined with a TCA or type 1C antiarrhythmic.[119] Although CYP2D6 has gained considerable notoriety for its role in drug interactions, gender-associated differences in CYP2D6 activity have not been reported.[70,127]

Gender differences have been identified for the CYP2C19 isoenzyme. Women have increased CYP2C19 activity.[70,128] Several antidepressants (citalopram, clomipramine, imipramine) and other medications (diazepam, propranolol) are primarily metabolized by the CYP2C19 isoenzyme.[125,129,130] As a result, these medications can be metabolized more rapidly in women, resulting in lower plasma concentrations. Because citalopram is initially metabolized by CYP2C19,[125] plasma concentrations may be relatively lower in women compared with those in men who receive the same dose.

There is some evidence that CYP1A2 activity may be lower in women.[131,132] Tertiary TCAs, fluvoxamine, and clozapine are psychotropic medications that are metabolized by CYP1A2.[125,129,130] Moreover, CYP1A2 is critical to the metabolism of tacrine, propranolol, theophylline, and warfarin.[125,129,130] Therefore, relatively greater plasma concentrations and possibly more adverse effects may occur in women compared with men receiving the same dose of these medications.

The most important gender difference may involve the CYP3A4 isoenzyme,[70] which constitutes more than 60% of the total P450 content within the liver.[133] This isoenzyme is responsible for the metabolism of numerous psychotropic medications, analgesics, calcium channel blockers, and steroid medications.[70,119,130] CYP3A4 activity appears to be influenced by both gender and age. Younger women have higher CYP3A4 activity in comparison with men or postmenopausal women.[70] As a result, premenopausal women would be expected to have lower concentrations of benzodiazepines in comparison with men or postmenopausal women for a benzodiazepine administered at the same dosing regimen.[125] The relatively lower plasma concentration may decrease the efficacy of benzodiazepines in premenopausal women. The higher CYP3A4 activity also may increase vulnerability for developing withdrawal phenomena and physiologic dependence in premenopausal women treated with benzodiazepines.[70]

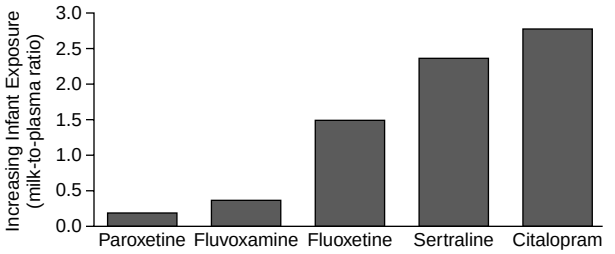
The relatively higher CYP3A4 activity noted in premenopausal women would be expected to contribute to lower plasma concentrations and potentially lower efficacy of other medications metabolized by this isoenzyme. This finding could have critical implications for premenopausal women receiving medication for seizures (carbamazepine), allergies (loratadine), hypertension (verapamil, nifedipine),

Table 3. Effect of Menstrual Cycle on Drug Metabolism[a]

Follicular phase
Decreased metabolism
Increased drug concentrations
Increased risk for adverse effects, toxicity
Mid-cycle (ovulation)
Increased oxidation
Maximal drug clearance
Luteal phase
Increased metabolism
Decreased drug concentrations
Possible increased risk for relapse

[a]Data from references 70, 107, 121, 139, and 140.

Figure 4. Milk-to-Plasma Ratios in Lactating Women Treated With Selective Serotonin Reuptake Inhibitors[a]



[a]Data from references 145 and 146.

pain (codeine), chemotherapy (tamoxifen), or infection (erythromycin, clarithromycin), or immunosuppressive medication (cyclosporine, cortisol).[125] In addition, age and gender should be considered when establishing dosing recommendations for women receiving antidepressants metabolized by the CYP3A4 isoenzyme, such as nefazodone or fluvoxamine.[125,134]

SPECIAL ISSUES WITH PSYCHOTROPIC MEDICATION

Oral Contraceptives and Hormone Replacement Therapy

Approximately one fourth of women in the United States between the ages of 15 and 44 years receive oral contraceptive medication.[135] Oral contraceptives generally contain estrogen (ethinyl estradiol, mestranol) and progestin. Most are highly protein bound, inhibit oxidative metabolism, and enhance conjugation.[124] With these features in mind, benzodiazepines (lorazepam, oxazepam, temazepam) metabolized by conjugation may be metabolized more rapidly in women who are taking oral contraceptives.[136,137] In contrast, benzodiazepines metabolized by oxidation (alprazolam, triazolam, diazepam) may achieve higher plasma concentrations in women also receiving oral contraceptives.[136] Oral contraceptives also reduce the activity of the hepatic CYP1A1/2 isoenzyme,[138] which may result in subsequent elevation of plasma concentrations of tertiary TCAs, propranolol, or clozapine if coadministered.[62,132,137]

Although one third of women between the ages of 50 and 65 years receive HRT, surprisingly few data are available concerning its impact on psychotropic medication. Yet, estrogen formulations used in HRT often are metabolized by CYP3A4.[125,130] Because fluvoxamine, fluoxetine, and nefazodone inhibit CYP3A4 activity,[125,130] HRT doses may need to be reduced if any of these antidepressants are coadministered to minimize adverse effects associated with elevated estrogen concentrations.

Menstrual Cycle: Impact on Drug Metabolism

Plasma concentrations of certain medications fluctuate during the menstrual cycle. Oxidative metabolism peaks at mid-cycle, resulting in maximum clearance of medications that are biotransformed by this pathway.[139,140] Antidepressant metabolism may decrease during the first half of the menstrual cycle (follicular phase), peak at mid-cycle (ovulation), and remain relatively high during the second half (luteal phase) of the cycle[70] (Table 3). Consequently, plasma concentrations, and perhaps adverse effects, may increase during the follicular phase. In contrast, decreased antidepressant concentrations during the luteal phase may be associated with reduced efficacy or relapse.

Pregnancy and Psychotropic Medication

Pregnancy is associated with substantial changes in pharmacokinetic characteristics of psychotropic medication.[70,141,142] Gastrointestinal motility is decreased, volume of distribution of medication is increased, and cardiac output is elevated during pregnancy.[70] The net impact of these changes is reduced plasma drug concentrations as pregnancy progresses. However, the physiologic changes associated with pregnancy generally are less problematic than issues concerning the potential risk versus benefit of using psychotropic medications during pregnancy and the postpartum period. Risks associated with psychotropic medications include teratogenic effects and direct neonatal toxicity.[143]

Lactation and Psychotropic Medication

Available data suggest that many psychotropic medications are excreted into breast milk. As summarized by Llewellyn and Stowe,[144] remarkably few data are available regarding the use of psychotropic medications during lactation. Most studies estimate that an extremely small amount (0.1%–6.2%) of the maternal dose is present in the infant,[144] and there are few reports of adverse effects in infants exposed to psychotropic medications in breast milk.[144] The milk-to-plasma ratio (higher ratios are associated with greater exposure to the infant) can be used to quantify the concentration of medication in milk compared with concentration in maternal serum. In evaluations of SSRIs, paroxetine has the lowest milk-to-plasma ratio[145,146] (Figure 4).

SUMMARY

Women have a substantially higher risk of developing anxiety disorders compared with men. Epidemiologic studies suggest that women have a 2- to 3-fold increase in the occurrence of panic disorder, PTSD, and GAD. Fluctuations in estrogen and progesterone levels can substantially influence the severity and course of anxiety disorders. In addition, women have lower gastric acidity, lower body weight, lower blood volume, and greater percentage of body fat compared with men, factors that may affect absorption and distribution of medications. Gender differences also affect metabolism by various cytochrome P450 enzymes and may result in clinically relevant alterations in plasma concentrations of psychotropic medications. Future investigations that focus on gender differences may provide valuable information for effective treatment strategies for women with anxiety disorders.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), citalopram (Celexa), clarithromycin (Biaxin and others), clomipramine (Anafranil and others), clozapine (Clozaril and others), cyclosporine (Neoral and others), diazepam (Valium and others) fluoxetine (Prozac), fluvoxamine (Luvox), loratadine (Claritin), lorazepam (Ativan and others), mestranol (Necon and others), nefazodone (Serzone), nifedipine (Adalat, Procardia), oxazepam (Serax and others), paroxetine (Paxil), phenytoin (Dilantin and others), propranolol (Inderal and others), sertraline (Zoloft), tacrine (Cognex), tamoxifen (Nolvadex), temazepam (Restoril and others), theophylline (Aerolate and others), triazolam (Halcion), venlafaxine (Effexor), verapamil (Calan and others), warfarin (Coumadin).

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