

A Primary Care Approach to Anxiety Disorders in Women

Generalized anxiety disorder and panic disorder

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It has long been recognized that most patients with mental illness are treated not in the psychiatric setting but in the general medical sector. For this reason, the term *de facto mental health system* was coined in reference to primary care.¹ Because anxiety disorders are the most common psychiatric disorders² and are two to three times more likely to occur in women,³ clinicians who treat female patients should be well educated in this area of mental health.

The following discussion of anxiety disorders in women is designed to give an overview of this very large topic, with a focus on how the disorders manifest differently in women and men (Table 1). First, we will review “medical mimics” of anxiety disorders—that is, medical illnesses and substance-induced disorders that can present with anxiety-like symptoms. Then, we will discuss diagnostic criteria, epidemiology, and treatment (Table 2) for two specific anxiety disorders: generalized anxiety disorder (GAD) and panic disorder.⁴ In an upcoming issue of *Women’s Health in Primary Care*, we will focus on the remaining anxiety disorders that are outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV): post-

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ABSTRACT: Before the diagnosis of an anxiety disorder can be made, substance-induced disorders and medical illnesses manifesting with anxiety symptoms must be considered. Patients with generalized anxiety disorder experience excessive anxiety and worry that are difficult to control. Prevalence among women is approximately twice that in men. Treatment options include selective serotonin reuptake inhibitors (SSRIs), buspirone, benzodiazepines, and cognitive behavior therapy. Panic attacks can be recognized by symptoms such as palpitations, sweating, and shortness of breath, which occur abruptly and reach a peak within 10 minutes. Panic is twice as common in women as it is in men, and women have a poorer prognosis. Treatment options include SSRIs, benzodiazepines, and cognitive behavior therapy. (*Women Health Primary Care* 2001;4(10):645-654)

traumatic stress disorder, obsessive-compulsive disorder, social phobia, and specific phobias.

MEDICAL MIMICS

Substance-induced disorders and medical illnesses manifesting with anxiety symptoms must be considered before the diagnosis of an anxiety disorder can be made. There is no

laboratory test or imaging study that confirms a psychiatric diagnosis. Clinicians are reliant upon their clinical judgment and index of suspicion to distinguish between anxiety disorders and the medical problems that mimic them. Pollard and Lewis⁵ suggest the following guidelines:

- ◆ A medical or substance-induced cause of anxiety is more likely when the first presentation is after age 40, there is fluctuation in the level of consciousness, or there is evidence of autonomic instability.
- ◆ An anxiety disorder is more likely when the patient is concerned about losing control, has a family history of anxiety problems, first presents between ages 18 and 45, has a recent or anticipated life event, or has agoraphobia.

SUBSTANCE-INDUCED

When evaluating a patient for anxiety, clinicians should obtain a good substance abuse history. Over-the-counter, prescription, or illegal substances may all cause anxiety. These substances include ephedrine,

pseudoephedrine, nicotine, caffeine, cocaine, and 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy).

An increasing number of women are taking herbal supplements that have side effects such as nervousness and insomnia. These supplements include St. John's wort (*Hypericum perforatum*), ma huang (*Ephedra*), and ginseng (*Panax ginseng*).⁶

times more likely than other women to have depression or any anxiety disorder.⁸ One study of people with cocaine dependence found anxiety disorders to be twice as prevalent in women as in men.⁹

CARDIAC

Supraventricular tachycardia (SVT) has many clinical similarities to panic disorder. One retrospective study by Lessmeier et al¹⁰ surveyed

palpitations are a prominent symptom. Patients who have atrioventricular nodal reentrant tachycardia, the most common type of SVT, have a normal electrocardiogram between paroxysms. However, the electrocardiograms of patients who have Wolff-Parkinson-White syndrome show a characteristic preexcitation wave (Δ wave) between attacks.¹¹ In a review of the early electrocardiograms of patients with SVT who had not been given a diagnosis initially, 22% had ventricular preexcitation waves that had gone unrecognized.¹⁰

Other cardiac problems that may present with anxiety symptoms include myocardial infarction (MI), coronary insufficiency, congestive heart failure, and anemia. Evidence suggests that patients with MI and lactic acidosis may have a catecholamine release from the locus ceruleus, which causes feelings of anxiety.¹²

Patients diagnosed with mitral valve prolapse frequently present with palpitations and chest pain. Despite a high rate of co-occurrence between mitral valve prolapse and panic disorder, a cause-effect relationship has never been definitively established.¹³

PULMONARY

While asthma attacks and panic attacks share many of the same symptoms, it is usually possible to distinguish between the two by history. One study found that when wheezing, coughing, and mucus production were present, asthma was the most likely diagnosis (sensitivity of more than 90%, specificity of more than 70%).¹⁴ However, it can be challenging to diagnose anxiety disorders in patients with known asthma or chronic obstructive pulmonary disease. Panic is more common in these patients than in normal controls.¹⁵ Co-occurrence of untreated panic and obstructive lung disease leads to more frequent use of as-needed

Table 1. Gender differences in anxiety disorders

<p>Generalized anxiety disorder</p> <ul style="list-style-type: none"> ◆ The rates of generalized anxiety disorder in women are approximately twice those found in men. ◆ Limited data suggest that anxiety symptoms may worsen in women premenstrually and postpartum. ◆ Women with generalized anxiety disorder are more likely than men to have comorbid psychiatric disorders. <p>Panic disorder</p> <ul style="list-style-type: none"> ◆ Not only is panic disorder twice as common in women, but women are twice as likely as men to have panic with agoraphobia. ◆ Women with panic disorder have a poorer prognosis than men do. Three years after successful treatment, 39% of women and 17% of men have symptom recurrence.
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Withdrawal of alcohol, opiates, or benzodiazepines should also be considered. Patients who take alprazolam, a short-acting benzodiazepine, to treat anxiety may have withdrawal symptoms between doses. Caffeine is a commonly ingested substance, and somatic manifestations of caffeinism are similar to symptoms of anxiety disorders. Such manifestations include diuresis, insomnia, anxiety, withdrawal headache, diarrhea, tachycardia, and tremulousness.⁷ Clinical experience shows that some women take methylphenidate—prescribed to their children—as an appetite suppressant and as treatment for depression and decreased concentration.

Women with anxiety disorders often have comorbid substance abuse. In one study, women with alcohol disorders were two to three

107 patients with known reentrant SVT in an electrophysiology office. In this cohort, 88% of patients experienced four or more symptoms of panic, and 67% fulfilled the DSM-IV criteria for panic disorder. The diagnosis of SVT was initially unrecognized in 55% and remained so for a median of 3.3 years. Before the SVT was discovered, women were about twice as likely as men were to carry the diagnosis of panic or anxiety. This study also found that diagnosis was much more likely to be made by an event monitor than by a Holter monitor. Anxiety symptoms resolved in 86% of patients who received appropriate treatment for SVT.

This study illustrates the importance of considering SVT in patients with anxiety symptoms. We suggest a low threshold for event monitor evaluation, especially if

medications and corticosteroids, more hospital admissions, and longer hospital stays.¹⁴

ENDOCRINE

Hyperthyroidism is perhaps the most well-known medical mimic of anxiety disorders. The epidemiology and symptomatology of anxiety disorders and hyperthyroidism are similar. Women are 10 times more likely than men are to have hyperthyroidism, and the disease is most common at ages 30 through 40 years.¹⁶ It is reasonable to check the level of thyroid-stimulating hormone in all patients who present with symptoms of anxiety.

Menopause is another common cause of insomnia, fatigue, and irritability. A careful history is required to differentiate hot flashes and other symptoms of menopause from anxiety disorders.

Pheochromocytoma causes catecholamine release and may be misdiagnosed as anxiety.¹⁷ Clues pointing to pheochromocytoma include hypertension, abdominal pain, and anxiety that are refractory to treatment. Hypertension may be persistent, or it may present only during a catecholamine surge. Therefore, even in the absence of elevated blood pressure, clinicians may see some evidence of the long-term consequences of hypertension, such as retinopathy and congestive heart failure.¹⁸

Consider the diagnosis of congenital adrenal hyperplasia (CAH) in women who have anxiety with hirsutism, infertility, and irregular menses. CAH is an autosomal recessive deficiency of steroidogenic enzymes that is present in 1% of the population.¹⁹ This disorder causes the accumulation of dehydroepiandrosterone (DHEAS)—an antagonist of the γ -aminobutyric acid A (GABA [A]) receptor in the brain—which has potent anxiogenic effects. In one study of 12 patients with refractory anxiety disorders and CAH, anxiety levels

decreased by 55% after appropriate treatment for CAH.¹⁹

Other medical conditions to consider include hypoglycemia, which is seen most commonly in patients taking diabetes medication. Hypercalcemia and hypocalcemia associated with abnormal parathyroid function may manifest with anxiety and irritability. Also consider Addison's disease, Cushing's syndrome, pulmonary embolus, temporal lobe epilepsy, vertigo, and carcinoid when evaluating a patient with unexplained anxiety symptoms.

GENERALIZED ANXIETY DISORDER

DEFINITION AND CRITERIA

People with GAD have excessive anxiety and worry that are difficult to control. According to the *DSM-IV*, symptoms must be present for more days than not for a six-month

period, and the patient must not meet criteria for another anxiety disorder.⁴ Worrying is associated with at least three of the following: restlessness or feeling keyed up or on edge, easy fatigability, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. Women with GAD worry excessively about multiple areas of life, such as school or work performance, marriage, social acceptance, finances, and health. As for any psychiatric diagnosis, these symptoms must impair a person's ability to function in order to meet the diagnostic criteria. Medical causes and substance-induced disorders must be ruled out.

EPIDEMIOLOGY AND IMPACT ON SOCIETY

In women, GAD has a lifetime prevalence rate of 6.6% and a one-year prevalence rate of 4.3%.²⁰

Table 2. Treatment options for anxiety disorders in women

Condition	Psychotherapy	Pharmacotherapy (typical starting dosage)
Generalized anxiety disorder	Cognitive behavior therapy Cognitive therapy	Venlafaxine (standard dosage is 37.5 mg bid, extended-release dosage is 37.5 mg/d)
		Buspirone (5.0 mg bid) (use the triple-scored 15-mg tablet)
		Benzodiazepines (for short periods) (clonazepam 0.5 mg twice daily as needed, and at bedtime)
		Selective serotonin reuptake inhibitors (low starting dosages)
		Tricyclic antidepressants (low starting dosages)
Panic disorder	Cognitive behavior therapy	Trazodone (25 to 50 mg/d at bedtime)
		Selective serotonin reuptake inhibitors (low starting dosages)
		Tricyclic antidepressants (low starting dosages)
		Benzodiazepines (until the antidepressant has time to take effect) (clonazepam 0.5 mg twice daily as needed, and at bedtime)

These rates are approximately twice those found in men.²⁰

GAD is a chronic disorder with periodic exacerbations. Symptoms tend to worsen during times of stress and lessen when the stressful period has passed. Limited data suggests that anxiety symptoms may worsen premenstrually and postpartum.²¹ The disorder is more common in unmarried people, racial or ethnic minorities, and people of low socioeconomic status.²¹

Despite the chronic course associated with GAD, very few studies have investigated long-term outcomes. The available data show that half of patients still have moderate symptoms at four- to 20-years' follow-up. Since the mean age of onset is late teens and early 20s, GAD may persist for a large portion of a patient's life.²²

Women who have GAD are more likely than men are to have comorbid psychiatric disorders.²¹ In one study, the most common comorbid diagnoses were panic disorder with agoraphobia (41%), major depression (37%), and social phobia (32%).²³ Alcohol dependence is another common comorbidity in women.²¹ GAD can be especially difficult to diagnose in this setting since GAD and alcohol withdrawal have similar symptoms. In addition, women are often secretive about their use of alcohol and may be reluctant to disclose it to their clinician.

TREATMENT

Venlafaxine and buspirone have the most clinical evidence to support their use. One study comparing the two medications found that both were superior to placebo and that venlafaxine was superior to buspirone.²⁴ However, buspirone may be better tolerated since it lacks any sexual side effects. In order to achieve maximal response to buspirone, a dosage of 30 mg/d is recommended.²⁵

Benzodiazepines are effective,

especially in relieving acute symptoms. Although studies show that benzodiazepines are more effective in the initial treatment period, paroxetine, tricyclic antidepressants (TCAs), buspirone, and trazodone reached comparable effi-

this indication.²⁵

TCAs are also effective, but they are not usually first-line therapy due to their side effects. When treatment is started with either an SSRI or a TCA, patients may experience an initial period of increased anxiety symptoms.³⁰ It is recommended, therefore, that the starting dose be half that recommended for depression, and that the dose be slowly increased over time.³¹ The general rule of thumb is to start at a low dosage and titrate up slowly to avoid possible side effects of overstimulation.

Non-pharmacologic therapy for GAD is also beneficial. In a recent review of the literature, Falsetti and Davis³² found cognitive behavior therapy and cognitive therapy to be superior to placebo, with improvement rates ranging from 30% to 60%. The studies that have compared medications (benzodiazepines and TCAs) to psychotherapy have found that medications show more immediate relief, but cognitive behavior therapy achieves more long-term results. Studies are limited, however, and more research is needed before definitive conclusions can be made.³²

Table 3. Signs and symptoms of a panic attack

<ul style="list-style-type: none"> ◆ Palpitations ◆ Sweating ◆ Trembling ◆ Shortness of breath ◆ Choking ◆ Chest pain ◆ Nausea or sudden gastrointestinal symptoms ◆ Dizziness or lightheadedness ◆ Derealization ◆ Fear of losing control ◆ Fear of dying ◆ Paresthesias ◆ Chills ◆ Flushing
<p>Data extracted from the American Psychiatric Association. <i>Diagnostic and Statistical Manual of Mental Disorders</i>. 4th ed. 1994.⁴</p>

cacy within several weeks.²⁶⁻²⁸ Alcohol-dependent disorders are common in patients with GAD, and alcohol and benzodiazepines have additive central nervous system effects. Long-term use of benzodiazepines should be avoided. Benzodiazepines should only be used for short periods when symptoms have worsened due to life stressors.

Paroxetine is an effective treatment and is the only selective serotonin reuptake inhibitor (SSRI) studied in a large multicenter placebo-controlled trial. Symptomatic improvement was dose-dependent.²⁹ Although no other SSRIs have been studied in large trials, mental health providers believe there is a general class response to all SSRIs, and they are increasingly prescribing them for

PANIC DISORDER

DEFINITION AND CRITERIA

Panic attacks can be recognized by characteristic signs and symptoms that occur abruptly and reach a peak within 10 minutes. According to the *DSM-IV*, a patient must have at least four of the signs and symptoms listed in Table 3. In addition to these symptoms, there is an intense apprehension or fear that can range from a feeling of losing control to the thought that death is imminent. Not all panic attacks occur in patients with panic disorder. Panic attacks may occur alone, or they may be symptoms of other anxiety disorders (Table 4). In order to meet the criteria for panic disorder, a panic attack must be followed by at least one month of per-

sistent concern about having another attack.

Because panic manifests with somatic complaints, the disorder can mimic many medical conditions. Women with panic disorder may present with what appears to be MI, irritable bowel syndrome, vertigo, near syncope, cardiac arrhythmias, hypoglycemia, asthma, or viral illness. The main clinical difference between a medical condition and panic disorder is the overpowering fear experienced in panic disorder.

Palpitations in the absence of a cardiac arrhythmia are common in patients with panic disorder. Evidence suggests that most people who have true cardiac arrhythmias do not perceive them and that patients with panic may have an enhanced ability to perceive sinus rhythm and ectopic beats. This ability may contribute to the sensation of palpitations.³³ Such enhanced perception is congruent with the general state of hyperarousability seen in patients with anxiety disorders.

Panic symptoms may occur unexpectedly or may be triggered by specific situations, locations, or certain emotional states. Some patients experience attacks at night that awaken them from sleep.³⁴ Panic attacks are so worrisome that

patients often change their behavior to try and avoid having another one.

Such changes may lead to agoraphobia, a condition in which patients have marked anxiety about being in a place or situation in which escaping or obtaining help might be difficult if an attack were to occur. Agoraphobia can be debilitating and is present in one third to one half of patients with panic disorder.³⁵ Panic disorder with agoraphobia is more difficult to treat than is panic disorder alone, and the agoraphobic symptoms often continue even after the panic symptoms have abated.³⁶

EPIDEMIOLOGY AND IMPACT ON SOCIETY

The one-month prevalence of panic disorder in the general population is 1% to 2% for men and 2% to 5% for women. Not only is panic twice as common in women, but women are twice as likely as men are to have panic with agoraphobia.³⁶ These statistics are true across cultural boundaries.³⁵ In addition, women have a poorer prognosis than men do. One study showed that three years after remission, 39% of women and 17% of men had symptom recurrence lasting four to eight weeks.³⁷ Panic disorder is responsible for more

work impairment than depression or any other anxiety disorder. One study showed 4.9 work-cut-back days per month, compared to 2.8 for depression.³⁸

TREATMENT

The treatment of panic disorder with medications can be difficult since a characteristic feature of the condition is fear of adverse medical events and heightened sensitivity to somatic sensations.³⁴ These symptoms make compliance more difficult because the patient with panic may fear taking medications and will often be more sensitive to side effects.

Multiple studies have shown that SSRIs effectively treat panic disorder. Paroxetine, sertraline, fluoxetine, and fluvoxamine have all been shown to be superior to placebo in clinical trials.^{30,39-41} Imipramine and clomipramine, both TCAs, are also effective, but they have more side effects.⁴² Doses of antidepressants used for panic attacks, like those used for GAD, should be low initially and titrated upward as necessary.

Benzodiazepines are also effective for panic disorder. However, this class is not the best choice for long-term maintenance therapy due to concerns about dependence and withdrawal. Instead, benzodi-

Table 4. Panic attacks in anxiety disorders

Diagnosis*	Spontaneous panic attacks	Situational panic attacks	Anticipatory anxiety	Symptoms of autonomic arousal	Phobic avoidance
Panic disorder	+++	+/-	+++	+++	+
Agoraphobia	+/-	+/-	+++	++	+++
Social phobia	-	++	++	++	+++
Specific phobia	+/-	+++	++	++	+++
Post-traumatic stress disorder	+/-	+	+/-	+++	+
Generalized anxiety disorder	+/-	+/-	+/-	+	+/-

+ to +++, present; -, not usually present; +/-, frequently present but not needed for diagnosis.

* Social phobia, specific phobias, and post-traumatic stress disorder will be discussed in an upcoming issue of *Women's Health in Primary Care*.

Adapted from Stahl. *Essential Psychopharmacology*. 2000⁴³ with permission of Cambridge University Press.

azepines are often used to abate symptoms of acute attacks and to decrease anxiety during the initial treatment period until the antide-

pressant has time to take effect.³¹ If a benzodiazepine is prescribed, many clinicians use one with a long half-life (such as clonazepam).

Although using medication with a shorter half-life is effective, the potential for dose-to-dose withdrawal and addiction seems greater.

One treatment approach for the primary care clinician is to start a low-dose SSRI and clonazepam concurrently. The patient may be told up front that the benzodiazepine will be given for only four to eight weeks to mask the increased anxiety symptoms that often occur during initial treatment with an SSRI. The patient may also be told that she will be referred to a psychiatrist if she is unable to be weaned from the benzodiazepine during that time. It has been our experience that most patients respond well to this approach. In addition, having the benzodiazepine in their possession often helps patients to overcome agoraphobia. The ability to medically abort an attack empowers patients to go places they may otherwise be afraid to go.

When used responsibly and infrequently, benzodiazepines can be a useful tool in the treatment of panic disorder. In patients who cannot discontinue benzodiazepine use, a psychiatric consultation is indicated.

Cognitive behavior therapy is also an excellent treatment option. In a review of the literature by the American Psychiatric Association, 88% of patients who received cognitive behavior therapy were panic-free after one year.³⁴ A National Institute of Mental Health consensus statement in 1991 concluded that both medical treatment and cognitive behavior therapy are standard treatments, and there is insufficient evidence that one is better than the other.

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PRIMARY POINTS

Anxiety Disorders in Women

A medical or substance-induced cause of anxiety is more likely when the first presentation is after age 40, there is fluctuation in the level of consciousness, or there is evidence of autonomic instability. An anxiety disorder is more likely when the patient is concerned about losing control, has a family history of anxiety problems, first presents between ages 18 and 45, has a recent or anticipated life event, or has agoraphobia.

An increasing number of women are taking herbal supplements that have side effects such as nervousness and insomnia. These include St. John's wort (*Hypericum perforatum*), ma huang (*Ephedra*), and ginseng (*Panax ginseng*).

Perhaps the most well-known medical mimic of anxiety disorders is hyperthyroidism. The epidemiology and symptomatology of anxiety disorders and hyperthyroidism are similar. It is reasonable to check the thyroid-stimulating hormone level in all patients who present with anxiety symptoms.

Women with generalized anxiety disorder worry excessively about multiple areas of life, such as school or work performance, marriage, social acceptance, finances, and health. Symptoms of generalized anxiety disorder tend to worsen during times of stress and lessen when the stressful period has passed.

Women with panic disorder may present with what appears to be myocardial infarction, irritable bowel syndrome, vertigo, near syncope, cardiac arrhythmias, hypoglycemia, asthma, or viral illness. The main clinical difference between a medical condition and panic disorder is the overpowering fear experienced in panic disorder.

When an antidepressant is used to treat anxiety or panic attacks, patients may experience an initial period of increased anxiety symptoms. It is recommended that the starting dose be half that recommended for depression and that the dose be slowly increased over time.

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