Major anxiety disorders are more prevalent in women than in men. Although the tendency toward anxiety disorders appears familial, other factors such as environmental influences can play a role in the risk for anxiety. This clinical review focuses on the pathophysiologic basis for anxiety disorders. It provides brief overviews of panic disorder, generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder. It also summarizes treatment options for patients with anxiety disorders.

The Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (Text Revision) (DSM-IV-TR)1 defines the five major anxiety disorders as social anxiety disorder (SAD), panic disorder (PD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD). Panic attacks, which represent an extreme form of anxiety, can occur in association with most of these anxiety disorders, though they are not typically associated with GAD. Lifetime prevalence rates of the major anxiety disorders range between approximately 3% (OCD) and 12% (SAD) and are approximately two times greater among women than among men.2,3

Pathophysiology of Anxiety Disorders
In the same way that behavioral traits are passed from parent to child, anxiety disorders tend to run through family structures. Studies comparing the risk of psychiatric illness in identical twins (who share 100% of their DNA) have found that in general, if one identical twin has a psychiatric condition, the risk that the other twin will have the same condition is approximately 50%.4 It therefore appears that nongenetic factors, including environmental influences occurring throughout the lifespan, must also contribute to the risk of developing an anxiety disorder.2,5

The human body attempts to maintain homeostasis at all times. Anything in the environment that disturbs homeostasis is defined as a stressor. Homeostatic balance is then reestablished by physiologic adaptations that occur in response to the stress response.5

The stress response in humans involves a cascade of hormonal events, including the release of corticotropin-releasing factor (CRF), which, in turn, stimulates the release of corticotropin, leading to release of the stress hormones (glucocorticoids and epinephrine) from the adrenal cortex. The glucocorticoids typically exert negative feedback to the hypothalamus, thus decreasing the release of CRF.6

The stress response is hardwired into the brain of the typical mammal and is most often triggered when survival of the organism is threatened. The primate stress response, however, can be triggered not only by a physical challenge, but also by the mere anticipation of a homeostatic challenge. As a result, when humans chronically and erroneously believe that a homeostatic challenge is about to occur, they enter the realm of neurosis, anxiety, and paranoia.5

The amygdala is the primary modulator of the response to fear- or anxiety-inducing stimuli. It is central to registering the emotional significance of stressful stimuli and creating emotional memories.7 The amygdala receives input from neurons in the cortex. This information is mostly conscious and involves abstract associations. Being stuck in traffic, in a crowded shopping mall, or on an airplane that is full may serve to trigger the anxiety response in a susceptible individual via this mechanism.

When activated, the amygdala stimulates regions of the midbrain and brain stem, causing autonomic hyperactivity, which can be correlated with the physical symptoms of anxiety. Thus, the stress response involves activation of the hypothalamic-pituitary-adrenal axis. This axis is hyperactive in depression and in anxiety disorders.8,9

Corticotropin-releasing factor, a 41 amino acid peptide, is a neurotransmitter within the central nervous system (CNS) that acts as a key mediator of autonomic, behavioral, immune, and...
endocrine stress responses. The peptide appears to be anxiogenic, depressogenic, and proinflammatory and leads to increased pain perception.\textsuperscript{10} \gamma-Aminobutyric acid (GABA) inhibits CRF release.\textsuperscript{6}

Glucocorticoids activate the locus caeruleus, which sends a powerfully activating projection back to the amygdala using the neurotransmitter norepinephrine. The amygdala then sends out more CRF, which leads to more secretion of glucocorticoids, and a vicious circle of feedback between the mind and the body results.\textsuperscript{5} Repeated stimulation of the amygdala results in strengthened communication across its synapses with other regions of the brain (ie, long-term potentiation).\textsuperscript{5}

Prolonged exposure of the CNS to glucocorticoid hormones eventually depletes norepinephrine levels in the locus caeruleus. As norepinephrine is an important neurotransmitter involved in attention, vigilance, motivation, and activity, the onset of depression may subsequently occur.

Serotonin appears to be involved in the pathogenesis of anxiety disorders as well. Agents that enhance serotonin neurotransmission may stimulate hippocampal 5-HT\textsubscript{1A} receptors, thus promoting neuroprotection and neurogenesis and exerting an anxiolytic effect.\textsuperscript{11}

GABA, the primary inhibitory neurotransmitter in the CNS, is another neurotransmitter believed to be inherently involved in the pathophysiology of anxiety disorders. Levels of GABA appear to be decreased in the cortex of patients with PD, compared with those in control subjects.\textsuperscript{12} Benzodiazepines facilitate GABA neurotransmission and therefore can improve anxiety.

Panic disorder
As discussed, panic attacks, defined as discrete periods of sudden symptom onset usually peaking in 10 minutes, can occur with most anxiety disorders.

The DSM-IV-TR criteria for panic attack are as follows\textsuperscript{1}:

- palpitations, pounding heart, or accelerated heart rate;
- sweating;
- trembling or shaking;
- sensations of shortness of breath or smothering;
- feeling of choking;
- chest pain or discomfort;
- nausea or abdominal distress;
- feeling dizzy, unsteady, lightheaded, or faint;
- derealization (feelings of unreality) or depersonalization (being detached);
- fear of losing control or going crazy;
- fear of dying;
- paresthesias;
- chills or hot flushes;
- one or more unexpected panic attacks;
- at least 1 month of worry, including change in cognition or behavior;
- presence or absence of agoraphobia;
- attacks not accounted for by another mental disorder, general medical condition, or effect of a substance.

Panic attacks must be differentiated from PD. Panic disorder as defined by the DSM-IV-TR includes:

- recurrent unexpected panic attacks;
- at least one of the attacks has been followed by 1 month (or more) of one or more of the following:
  - persistent concern about having additional attacks;
  - worry about the implications of their attacks or their consequences (eg, losing control, having a heart attack, going crazy); or
  - a significant change in behavior related to the attacks.

In general, individuals with PD may see up to ten practitioners before a correct diagnosis is made, have continuous increases in health care utilization spanning 10 years before diagnosis, and have a 5 to 8 times greater likelihood of being high users of health care.\textsuperscript{13-15}

Figure 1 summarizes pharmacotherapy for panic disorders.

Generalized Anxiety Disorder
Generalized anxiety disorder (GAD) is a chronic disorder that involves excessive anxiety and worry about a number of events for most days out of 6 months. Difficulty controlling the worry is paramount, with the individual manifesting physical and psychologic symptoms with the condition leading to significant distress or impairment.

In diagnosing GAD, physicians must rule out a general medical condition or substance abuse. Common somatic complaints of patients with GAD include muscle tension, cold or clammy hands, dry mouth, sweating, nausea, diarrhea, and urinary frequency. Psychologic symptoms include irritability, difficulty concentrating, and sleep disturbance.

In many individuals, subsyndromal manifestations of GAD are noticed in childhood and adolescence. The disorder manifests chronically with a pattern of waxing and waning symptoms and ongoing impairment in social function, potentially leading to the development of other anxiety, depressive, and substance abuse disorders.\textsuperscript{16,17} Treatment of GAD to remission is associated with a decreased risk of relapse.\textsuperscript{18}

Social Anxiety Disorder
The DSM-IV-TR criteria for SAD include fear or avoidance of social and performance situations or enduring such situ-

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**Checklist**

- Selective Serotonin Reuptake Inhibitors
  - Citalopram hydrobromide
  - Fluoxetine
  - Fluvoxamine maleate
  - Paroxetine hydrochloride
  - Sertraline hydrochloride
- Other Antidepressants
  - Monoamine oxidase inhibitors
  - Serotonin-norepinephrine reuptake inhibitors
- Benzodiazepines
  - Alprazolam
  - Clonazepam
- Tricyclic Antidepressants
  - Clomipramine
  - Imipramine hydrochloride
- Anticonvulsants
  - Valproate sodium
  - Gabapentin

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\textsuperscript{1} These criteria are from the DSM-IV-TR.
atons with anxiety or notable distress. Patients recognize SAD symptoms as being excessive or unreasonable; the condition is highly distressing or disabling. Common fears expressed by patients with SAD include participating in small groups; eating, drinking, or writing in public; talking to authority figures; performing or giving a talk; attending social events; working while being observed; meeting strangers or dating; using a public bathroom, and being the center of attention. Common somatic complaints presented by patients with SAD include trembling, shaking, blushing, sweating, stuttering, abdominal distress, and palpitations.

**Obsessive-compulsive disorder**

The DSM-IV-TR criteria for obsessions include unwanted thoughts, impulses, or images that cause great anxiety. These thoughts are not simply excessive worries about real life problems. Persons with obsessions attempt to ignore, suppress, or neutralize these thoughts, which are recognized as the product of their minds.

The DSM-IV-TR criteria for compulsions include repetitive behaviors or mental acts that those affected feel driven to perform. Compulsions are aimed at preventing or reducing distress or preventing a dreaded event, though the behavior is not realistically connected to the dreaded event and is clearly excessive.

**Posttraumatic Stress Disorder**

Criteria for the diagnosis of posttraumatic stress disorder (PTSD), as defined by the DSM-IV-TR,1 include exposure to a life-threatening or traumatic event that is persistently reexperienced. Individuals with PTSD avoid stimuli associated with the trauma, and they appear to have a numbing of general responsiveness and increased arousal. Posttraumatic stress disorder can also occur in individuals who witness another person’s traumatic event. Common stressors leading to PTSD include assaultive violence (eg, combat, rape, spousal abuse); other injury or shocking experience (eg, involvement in a fire, flood, or earthquake); and learning about trauma to a loved one.19

**Checklist**

- **Psychosocial Treatment**
  - Cognitive behavioral therapy
  - Other modes of therapy, such as:
    - individual
    - family
    - group

- **Pharmacotherapy**
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
  - Benzodiazepines
  - Buspirone hydrochloride
  - Other antidepressants:
    - venlafaxine hydrochloride extended release
    - nefazodone
    - mirtazapine

**Treatment Options for Patients With Anxiety Disorders**

*Figure 2* summarizes treatment options for patients with anxiety disorder.

Psychosocial treatment modalities may include cognitive behavioral therapy in which the individual is trained to identify recurrent negative, irrational thoughts that are correlated with the anxiety. Other treatment modalities involve desensitization modes of therapy, as well as supportive and interpersonal psychotherapy. Pharmacotherapy of anxiety disorders involves consideration of the known pharmacologic anxiolytic mechanisms of action.

Selective serotonin reuptake inhibitors include sertraline hydrochloride, paroxetine hydrochloride, fluvoxamine maleate, fluoxetine, citalopram hydrobromide, and escitalopram oxalate. Dual-acting antidepressants, such as venlafaxine (serotonin-norepinephrine reuptake inhibitor), mirtazapine (α₂-agonist/5-HT₂ and 5-HT₃ antagonists), monoamine oxidase (MAO) inhibitors, and the tricyclic antidepressants can also be highly effective for treating patients with the spectrum of anxiety disorders.

The benzodiazepines (eg, alprazolam and clonazepam) can provide immediate relief, especially in individuals with acute panic attacks. These agents work by facilitating GABA neurotransmission. Of particular interest is the compound tiagabine hydrochloride, which is a GABA reuptake inhibitor. Anticonvulsants can be particularly useful. Use of β-blockers can be helpful in performance anxiety, and buspirone hydrochloride can be effective for GAD.

Several agents have proved ineffective in treating panic attacks. These agents include bupropion hydrochloride, trazodone hydrochloride, buspirone hydrochloride, antipsychotics, (eg, olanzapine, risperidone) and β-blockers (eg, propranolol hydrochloride, atenolol).19

Use of MAOIs, tricyclic antidepressants, and benzodiazepines requires close monitoring and patient education, as there is a heightened risk of dietary and drug-drug interactions, lethality in overdose, and abuse or dependence.

**Comment**

Anxiety disorders, though ubiquitous, are responsive to treatment. By using knowledge of the pathophysiology, an astute clinician can implement pharmacologic regimens with various mechanisms of action, leading to a positive outcome. Anxiety disorders that are untreated or undertreated can chronically expose the CNS to long-term increased glucocorticoid levels, which can lead to functional changes in the CNS. Use of a multimodal approach in terms of pharmacologic mechanism of action will help in achieving and sustaining remission.

**References**


