ANXIETY DISORDERS

Anxiety is a normal, protective, psychological response to an unpleasant or threatening situation. The term *anxiety disorder* encompasses a variety of conditions that can either exist on their own or in conjunction with another psychiatric or physical illness.

Anxiety disorders are broadly divided into generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobias, separation anxiety disorder and illness anxiety disorder. Posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) were previously classified under the umbrella of anxiety disorders but are now considered to be separate illnesses.

❖ COMORBIDITY

More than 90% of individuals with an anxiety disorder have a lifetime history of one or more other psychiatric disorders. Depression is the most common comorbidity, followed by alcohol and substance use disorders, as well as other co-occurring anxiety disorders, especially GAD and PD.

❖ ETIOLOGY

Both genetic and psychosocial factors appear to play a role in the initiation and expression of anxiety disorders. Some researchers believe that stressful life events may have a strong role in the onset of anxiety disorders, especially in GAD and PD. It has been reported that those experiencing one or more negative life events have a threefold increased chance of developing GAD. Similar findings have been reported with PD.

❖ PATHOPHYSIOLOGY

Anxiety occurs when there is a disturbance of the arousal systems in the brain. Arousal is maintained by at least three interconnected systems: a general arousal system, an ‘emotional’ arousal system and an endocrine/autonomic arousal system. Excessive activity in the general arousal system, due to internal or external stresses, can lead to a state of hyperarousal as seen in anxiety. Emotional aspects of arousal, such as fear and anxiety, are contributed by the limbic system, which also serves to focus attention on selected aspects of the environment. There is evidence that increased activity in certain limbic pathways is associated with anxiety and panic attacks.

These arousal systems activate physical responses to arousal, such as increased muscle tone, increased sympathetic activity and increased output of anterior and posterior pituitary hormones. Inappropriate increases in autonomic activity are often

associated with anxiety states; the resulting symptoms (palpitations, sweating, tremor, etc.) may initiate a vicious circle that increases the anxiety.
Several neurotransmitters have been implicated in the arousal systems. Acetylcholine is the main transmitter maintaining general arousal, but there is evidence that heightened emotional arousal is particularly associated with noradrenergic and serotonergic activity. Drugs which antagonize such activity have anxiolytic effects. In addition, the inhibitory neurotransmitter γ-aminobutyric acid (GABA) exerts an inhibitory control on other transmitter pathways, and increased GABA activity may have a protective effect against excessive stress reactions. Many drugs which increase GABA activity, such as the benzodiazepines, are potent anxiolytics.

❖ CLINICAL PRESENTATION AND DIAGNOSIS OF GAD

⇨ General

Onset is typically in early adulthood. Anxiety emerges and dissipates more gradually than in PD.

⇨ Symptoms

•• Excessive anxiety or worry involving multiple events or activities occurring more days than not for at least 6 months
•• Difficulty controlling worry
•• Anxiety and worry associated with at least three of the following:
- Restlessness
- Easily fatigued
- Poor concentration or mind going blank
- Irritability
- Muscle tension
- Insomnia or unsatisfying sleep

•• The anxiety or worry causes significant distress or functional impairment and is NOT attributable to another substance, medical, or psychiatric condition

⇨ Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (to exclude organic causes such as thyrotoxicosis, excessive use of stimulant drugs such as caffeine and the possibility of alcohol dependence or withdrawal effects from benzodiazepines).

❖ TREATMENT: GENERALIZED ANXIETY DISORDER

⇨ Desired Outcomes

The goals of therapy for GAD are to acutely reduce the severity and duration of anxiety symptoms and restore overall functioning. The long-term goal is to achieve

and maintain remission. With a positive response to treatment, comorbid depressive symptoms should be minimized.

⇨ General Approach to Treatment

Patients with GAD may be managed with psychotherapy, pharmacotherapy, or both. Patients with severe symptoms resulting in functional impairment should receive antianxiety medication.

⇨ Nonpharmacologic Therapy

Nonpharmacologic therapy includes psychoeducation, exercise, stress management, and psychotherapy.

Psychoeducation should provide information on GAD and its management. Patients should be instructed to avoid stimulating agents, eg, caffeine, decongestants, diet pills, and excessive alcohol use. Regular exercise is also recommended.

Cognitive-behavioral therapy (CBT) is the most effective psychological therapy for GAD patients. It helps patients to recognize and alter patterns of distorted thinking and dysfunctional behavior. Treatment gains with CBT may be maintained for up to 1 year.

⇨ Pharmacologic Therapy

Antidepressants are the drugs of choice for chronic GAD because of a tolerable side-effect profile; no risk for dependency; and efficacy in common comorbid conditions, including depression, panic, obsessive compulsive disorder (OCD), and SAD. Benzodiazepines remain the most effective and commonly used treatment for short-term management of anxiety when immediate relief of symptoms is desired. They are also recommended for intermittent or adjunctive use during GAD exacerbation or for sleep disturbance during the initiation of antidepressant treatment. Buspirone and pregabalin are alternative agents for patients with GAD without depression. Hydroxyzine is usually adjunctive and is less desirable for long-term treatment because of side effects, eg, sedation and anticholinergic effects.

Patients with GAD should be treated to symptom remission.

»» *Antidepressants*

Antidepressants reduce the psychic symptoms (eg, worry and apprehension) of anxiety with a modest effect on autonomic or somatic symptoms (eg, tremor, rapid heart rate, and/or sweating). All antidepressants evaluated provide a similar degree of anxiety reduction. The onset of antianxiety effect is delayed 2 to 4 weeks. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are usually preferred over tricyclic antidepressants (TCAs) because of improved safety and tolerability.

Antidepressants modulate synaptic 5-HT, NE, and/or dopamine (DA) reuptake and receptor-activated neuronal signal transduction. These intracellular changes modify the expression of genes and proteins important in stress response (eg, glucocorticoid receptors, brain-derived neurotrophic factor, corticotropin-releasing hormone). Activation of these "stress-adapting" pathways may improve both somatic and psychic symptoms of anxiety.

Serotonin Norepinephrine Reuptake Inhibitors: Venlafaxine and duloxetine are approved by the FDA for the treatment of GAD. They alleviate anxiety with and without depression and have improved tolerability over TCAs. Venlafaxine is effective at doses 75 to 225 mg/day and maintains response with extended treatment. It is also effective for GAD in children and adolescents. The most common side effects reported in patients with GAD are nausea, somnolence, dry mouth, dizziness, sweating, constipation, and anorexia.
Duloxetine is similarly effective and tolerated as venlafaxine.

Selective Serotonin Reuptake Inhibitors: The SSRIs paroxetine, escitalopram, and sertraline have been shown to be significantly more effective than placebo in reducing anxiety symptoms in adults with GAD. Common side effects include somnolence, headache, nausea, dry mouth (paroxetine), diarrhea (sertraline), sweating (sertraline), decreased libido, ejaculation disorder, anorgasmia, and asthenia.

Tricyclic Antidepressants: Imipramine treatment of GAD results in a higher rate of remission of anxiety symptoms than treatment with trazodone or diazepam. Both antidepressants were more effective than diazepam or placebo in reducing psychic symptoms of anxiety. TCA use is limited by bothersome adverse effects (eg, sedation, orthostatic hypotension, anticholinergic effects, and weight gain). TCAs have a narrow therapeutic index and are lethal in overdose because of atrioventricular block.

»» ***Benzodiazepines***
Benzodiazepines are recommended for acute treatment of GAD when short-term relief is needed, as an adjunct during initiation of antidepressant therapy, or to improve sleep.
They are more effective for somatic symptoms than psychic symptoms. Major benzodiazepine disadvantages are lack of effectiveness for depression; risk for dependency and abuse; and potential interdose rebound anxiety, especially with short-acting benzodiazepines. They should be avoided in older adults and patients with current or past chemical dependency.
Benzodiazepines enhance transmission of the inhibitory neurotransmitter GABA through interaction with the GABAA-receptor complex. The most common side

effects of benzodiazepine therapy include CNS depressive effects (eg, drowsiness, sedation, psychomotor impairment, and ataxia) and cognitive effects (eg, poor recall and anterograde amnesia).
Discontinuation of benzodiazepines may be associated with withdrawal, rebound anxiety, and a high rate of relapse. Higher doses of benzodiazepines and a longer duration of therapy increase the severity of withdrawal and risk of seizures after abrupt or rapid discontinuation. Patients should be tapered rather than discontinued abruptly from benzodiazepine therapy to avoid withdrawal symptoms.

»» ***Pregabalin***
Pregabalin is a calcium channel modulator, and its anxiolytic properties are attributed to its selective binding to the α-2-delta subunit of voltage-gated calcium channels. Pregabalin was effective for both somatic and psychic symptoms of anxiety with onset of effect similar to that of alprazolam. It should be used cautiously in patients with a current or past history of substance abuse. It is not beneficial for depression or other anxiety disorders.

»» ***Alternative Agents***
Hydroxyzine, buspirone, and second generation antipsychotics (SGAs) are alternative agents. Hydroxyzine may be effective for acute reduction of somatic symptoms of anxiety but not for psychic features of anxiety, depression, or other common comorbid anxiety disorders.
Buspirone, a 5-HT1A partial agonist, is thought to exert its anxiolytic effects by reducing presynaptic 5-HT firing. It has a gradual onset of action (ie, 2 weeks) and does not provide immediate anxiety relief. Buspirone is well tolerated and does not cause sedation. The most common side effects include dizziness, nausea, and headaches.
The SGAs, quetiapine, olanzapine, and risperidone have demonstrated benefit in GAD. Risperidone and olanzapine may improve treatment outcomes in patients with inadequate response to initial pharmacotherapy. SGAs are associated with a risk of weight gain, sedation, fatigue, and extrapyramidal symptoms in anxiety patients.

❖ CLINICAL PRESENTATION AND DIAGNOSIS OF PD

⇨ General

Typically presents in late adolescence or early adulthood. Onset in older adults raises suspicion of a relationship to medical disorders or substance use. Laboratory evaluation must be driven by history and physical examination.

⇨ Symptoms

Recurrent, unexpected panic attacks. A panic attack is an abrupt surge of intense fear or discomfort peaking within minutes, and with four or more of the following symptoms:

•• Palpitations or rapid heart rate
•• Sweating
•• Trembling or shaking
•• Sensation of shortness of breath or smothering
•• Feeling of choking
•• Chest pain or discomfort
•• Nausea or abdominal distress
•• Feeling dizzy or lightheaded
•• Chills or hot flushes
•• Paresthesias
•• Derealization or depersonalization
•• Fear of dying
•• Fear of losing control or "going crazy"

At least one of the attacks has been followed by 1 month or more of one or both:

•• Persistent concern or worry about additional attacks
•• Significant maladaptive change in behavior related to the attacks (eg, avoidance)

❖ TREATMENT: PANIC DISORDER

⇨ Desired Outcomes

The main objectives of treatment are to reduce the severity and frequency of panic attacks, reduce anticipatory anxiety and agoraphobic behavior, and minimize symptoms of depression or other comorbid disorders. The long-term goal is to achieve and sustain remission and restore overall functioning.

⇨ General Approach to Treatment

Treatment options include medication, psychotherapy, or a combination of both. In some cases, pharmacotherapy will follow psychotherapy treatments when full response is not realized.

Patients with panic symptoms without agoraphobia may respond to pharmacotherapy alone. Agoraphobic symptoms generally take longer to respond than panic symptoms. *The acute phase of PD treatment lasts about 12 weeks and should markedly reduce or eliminate panic attacks and minimize anticipatory anxiety and phobic avoidance. Treatment should be continued to prevent relapse for an additional 12 to 18 months before attempting discontinuation.*

⇨ **Nonpharmacologic Therapy**

Patients with PD should avoid stimulant agents (eg, decongestants, diet pills, and caffeine) that may precipitate a panic attack.

CBT generally includes psychoeducation, self-monitoring, countering anxious beliefs, exposure to fear cues, and modification of anxiety-maintaining behaviors. Exposure therapy is useful for patients with phobic avoidance. CBT is considered a first-line treatment of PD, with efficacy similar to that of pharmacotherapy.

⇨ **Pharmacologic Therapy**

Patients with PD may be treated with TCAs, SSRIs, SNRIs, or MAOIs, as well as benzodiazepines with similar effectiveness, but SSRIs have become the treatment of choice.

»» ***Antidepressants***

Antidepressants typically require 4 weeks for onset of antipanic effect, with optimal response at 6 to 12 weeks. Reduction of anticipatory anxiety and phobic avoidance generally follows improvement in panic symptoms. *PD patients are more likely to experience stimulant-like side effects of antidepressants than patients with major depression. Antidepressants should be initiated at lower doses in PD patients than in depressed patients.* Target doses are similar to those used for depression. *Antidepressants should be tapered when treatment is discontinued to avoid withdrawal symptoms, including irritability, dizziness, headache, and dysphoria.*

Tricyclic Antidepressants: Treatment with imipramine, leaves 45% to 70% of patients panic free. Desipramine and clomipramine are also effective. However, TCAs are considered second or third-line pharmacotherapy because of poorer tolerability and toxicity on overdose.

PD patients taking TCAs may experience anticholinergic effects, orthostatic hypotension, sweating, sleep disturbances, dizziness, fatigue, sexual dysfunction, and weight gain. Stimulant-like side effects occur in up to 40% of patients.

Selective Serotonin Reuptake Inhibitors: SSRIs are the drugs of choice for patients with PD. The most common side effects of SSRIs include headaches, irritability, nausea and other gastrointestinal complaints, insomnia, sexual dysfunction, increased anxiety, drowsiness, and tremor.

Serotonin Norepinephrine Reuptake Inhibitors: Venlafaxine, in dosages of 75 to 225 mg/day, reduced panic and anticipatory anxiety in short-term controlled trials and prevented relapse with extended treatment over 6 months. The most common

side effects include anorexia, dry mouth, constipation, somnolence, tremor, abnormal ejaculation, and sweating.

Monoamine Oxidase Inhibitors: MAOIs are reserved for patients who are refractory to other treatments. They have significant side effects that limit adherence. Additionally, patients must adhere to dietary restriction of tyramine and avoid sympathomimetic drugs to avoid hypertensive crisis.

»» ***Benzodiazepines***

Benzodiazepines are effective antipanic agents with significant effects on anticipatory anxiety and phobic behaviors.

The risk for dependence and withdrawal and lack of efficacy for depression are significant concerns for long-term treatment of patients with PD. Patients with PD experience greater rebound anxiety and relapse when discontinuing benzodiazepines than do patients with GAD. Tapering should be done at a slower rate and over a more extended period of time than with other anxiety disorders.

The dose of benzodiazepine required for improvement generally is higher than that used in other anxiety disorders, and this may explain why high-potency agents such as alprazolam and clonazepam generally are preferred.

The most common side effects of benzodiazepines are sedation, fatigue, and cognitive impairment. Benzodiazepines should be avoided in patients with current or past substance abuse or dependence or sleep apnea. Additionally, caution should be used in older adults because they have more pronounced psychomotor and cognitive side effects.

»» ***β-Blockers***

Pindolol 25 mg three times a day is an effective adjunctive treatment with an SSRI. Propranolol 120 to 240 mg/day has been found equivalent to alprazolam in reduction of panic attacks. β-blockers are not expected to reduce psychic anxiety or avoidance behavior. Additionally, heart rate and blood pressure reduction are dose-related adverse events that may limit use.

❖ CLINICAL PRESENTATION AND DIAGNOSIS OF SAD

⇨ General

SAD is a chronic disorder that begins in adolescence and occurs with significant functional impairment and high rates of comorbidity.

Individuals have marked fear or anxiety about one or more social situations where they are exposed to possible scrutiny or negative evaluation (eg, common social interactions, conversation, eating, drinking or performing). SAD differs from specific phobia, in which the fear and anxiety are limited to a particular object or situation

(eg, insects, heights, public transportation). In children, the anxiety must be present in peer settings, not just in interactions with adults.

⇨ **Symptoms**

•• The individual fears acting in a way or showing anxiety that will be negatively evaluated (ie, humiliating or embarrassing or lead to rejection or offend others)

•• Social situations almost always provoke fear or anxiety and are avoided or endured with intense fear or anxiety. Children may express fear or anxiety by crying, tantrums, freezing, clinging or failing to speak in social situations.

The fear or anxiety is

•• out of proportion to the actual threat posed by the social situation;

•• persistent, typically lasting for 6 months or more;

•• causes clinically significant distress or impairment in social, occupational, or other area of functioning;

•• not attributable to physiological effects of a substance or another medical condition; and

•• not better explained by the symptoms of another mental disorder (eg, panic disorder, body dysmorphic disorder, or autism spectrum disorder)

❖ **TREATMENT: SOCIAL ANXIETY DISORDER**

⇨ **Desired Outcomes**

The goal of acute treatment is to reduce physiologic symptoms of anxiety, fear of social situations, and phobic behaviors. Patients with comorbid depression should have a significant reduction in depressive symptoms. The long-term goal is to restore social functioning and improve the patient's quality of life.

⇨ **General Approach to Treatment**

Patients with SAD may be managed with pharmacotherapy or psychotherapy. Children with SAD should be offered psychotherapy first. Many patients will not achieve a full response.

⇨ **Nonpharmacologic Therapy**

Patient education on disease course, treatment options, and expectations is essential. CBT targets avoidance-learning and negative thinking patterns associated with social anxiety. CBT is effective for reducing anxiety and phobic avoidance and leads to a greater likelihood of maintaining response after treatment discontinuation than does pharmacotherapy.

⇨ **Pharmacologic Therapy**

SSRIs are considered the drugs of choice based on their tolerability and efficacy for SAD and comorbid depression if present. The onset of response for antidepressants

may be as long as 8 to 12 weeks. Patients responding to medication should be continued on treatment for at least 1 year. Many patients relapse when medication is discontinued, and there are no clear predictive factors for who will maintain response. Some patients may elect more longterm treatment owing to fear of relapse.

»» ***Selective Serotonin Reuptake Inhibitors and Venlafaxine***

SSRIs and SNRIs improve social anxiety and phobic avoidance and reduce overall disability. The initial dose of SSRI is similar to that used in depression. Patients with comorbid PD should be started on lower doses. When discontinuing SSRIs, the dose should be tapered slowly to avoid withdrawal symptoms.

Side effects of SSRIs in SAD are similar to those seen in depression and include nausea, sexual dysfunction, somnolence, and sweating.

Venlafaxine extended release, in doses of 75 to 225 mg/day, has similar efficacy to SSRIs. Doses should be tapered slowly when discontinuing. Common side effects are anorexia, dry mouth, nausea, insomnia, and sexual dysfunction.

»» ***Monoamine Oxidase Inhibitors and Reversible Inhibitors of Monoamine Oxidase***

Phenelzine, effective in 64% to 69% of SAD patients, is generally reserved for treatment-refractory patients owing to dietary restrictions, drug interactions, and side effects. The RIMAs brofaramine and meclobemide are also effective.

»» ***Alternative Agents***

Benzodiazepines: Benzodiazepines are used commonly in SAD; however, limited data support their use. Clonazepam was shown effective for social anxiety, fear, and phobic avoidance, and it reduced social and work disability during acute treatment.

Long-term treatment is not desirable for many SAD patients because of the risk of withdrawal and difficulty with discontinuation, cognitive side effects, and lack of effect on depressive symptoms.

Anticonvulsants: Gabapentin and pregabalin, structurally similar anticonvulsants, have each demonstrated modest benefit. Gabapentin was titrated to a maximum dose of 3600 mg/day and pregabalin to 600 mg/ day. While both medications have good tolerability, they should be considered for patients with inadequate response to SSRI/SNRIs.

β-Blockers: β-blockers decrease the physiologic symptoms of anxiety and are useful for reducing performance anxiety. Propranolol (20-40 mg) or atenolol (50-100mg) should be administered 1 hour before a performance situation. β-blockers are not useful in SAD.