

## Generalized Anxiety Disorder

### Epidemiology

Anxiety disorders are more prevalent among women than men (2:1).

Prevalence rates across the anxiety spectrum increase from the younger age group (18–29 years) to older age groups (30–44 and 45–59 years); however, rates are substantially lower for those older than age 59 years.

### Definitions

**Generalized anxiety disorder (GAD)** is characterized by excessive and persistent worrying that is hard to control, causes significant distress or impairment, and occurs on most days of at least **six months**.

**Social anxiety disorder (SAD)**, also known as **social phobia**, is a common disorder characterized by excessive fears of scrutiny, embarrassment, and humiliation in social or performance situations, leading to significant distress or impairment in functioning.

**Panic disorder (PD)**: Panic attacks classically present with spontaneous, discrete episodes of intense fear that begin abruptly and last for several minutes to an hour. In **panic disorder**, patients experience recurrent panic attacks, at least some of which are not triggered or expected, and one month or more of either worry about future attacks/consequences, or a significant maladaptive change in behavior related to the attacks, such as avoidance of the precipitating circumstances.

### Depression (Unipolar major depression (major depressive disorder))

Is diagnosed in patients with a history of at least one major depressive episode and no history of mania or hypomania; in addition, the depressive episode is not caused by medications or concurrent general medical conditions.

A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide; at least one of the symptoms must be depressed mood or anhedonia.

### Natural history of the disease

PD and GAD have a median age of onset of 24 and 31 years, respectively, whereas SAD develops earlier (median age 13 years). Although GAD and PD may not manifest fully until adulthood, as many as half of adult anxiety patients report subthreshold symptoms during childhood.

Anxiety disorders are chronic, and symptoms tend to wax and wane, with fewer than one-third of patients experiencing spontaneous symptom remission.<sup>6</sup> The risk for relapse and recurrence of symptoms is also high for anxiety disorders.

Remission, if achieved with treatment, is most likely to occur within the first 2 years of an index episode.<sup>6</sup> Similarly, the highest rates of relapse are within the same timeframe. This suggests that many patients need ongoing maintenance treatment. Rates of remission and relapse do not appear to vary by sex.

### **Comorbidity**

Depression is the most common comorbidity, followed by alcohol and substance use disorders, as well as other cooccurring anxiety disorders, especially GAD and PD.

Comorbid psychiatric illness is associated with lower rates of remission and higher rates of relapse.

### **Clinical Presentation and Diagnosis of GAD**

#### ***General***

Onset is typically in early adulthood. Anxiety emerges and dissipates more gradually than in PD. Laboratory evaluation usually is reserved for later onset, atypical presentation, or poor response to treatment.

#### ***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

### **Treatment**

#### ***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.
- Treatment should be individualized based on:
  - symptom severity
  - comorbid illnesses
  - medical status
  - age
  - patient preference.
- Patients with severe symptoms resulting in functional impairment should receive antianxiety medication.

### **Nonpharmacologic Therapy**

Nonpharmacologic therapy includes:

- Psychoeducation
- Exercise
- Stress management
- 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. A recent trial in children with GAD suggests **the combination of CBT and medication is superior to either treatment alone.**

## Pharmacologic Therapy

Antidepressants, benzodiazepines, pregabalin, buspirone, hydroxyzine, and the second-generation antipsychotics (SGAs) have controlled clinical trial data supporting their use in GAD.

**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. Although supporting data are lacking, recent guidelines recommend continuing treatment for **1 year**.

### 1. Antidepressants

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.

#### *a. Serotonin Norepinephrine Reuptake Inhibitors*

Venlafaxine and duloxetine are approved by the Food and Drug Administration (FDA) for the treatment of GAD.

They alleviate anxiety with and without depression and have improved tolerability over TCAs.

It is also effective for GAD in children and .

For patients with concurrent pain syndromes, duloxetine has been found to improve anxiety, pain, and functional impairment more than placebo.

#### *b. 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.

Citalopram is efficacious in the treatment of GAD in the elderly.

The SSRIs, sertraline, fluoxetine, and fluvoxamine have demonstrated benefits in children and adolescents with GAD and are the preferred pharmacologic treatment in this population.

*c. Tricyclic Antidepressants*

Imipramine treatment of GAD results in a higher rate of remission of anxiety symptoms than treatment with trazodone or diazepam.

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.

*d. Novel Antidepressants*

Mirtazapine, an  $\alpha$ -2 adrenergic antagonist and postsynaptic serotonin receptor antagonist, is an effective antidepressant but has not been extensively evaluated in anxiety disorders. It causes sedation and weight gain.

Bupropion, a dopamine and norepinephrine reuptake-inhibitor, lacks the common antidepressant side effects of weight gain and sexual dysfunction.

Bupropion has not been studied or used extensively in anxiety disorders owing to its stimulating effects that would be expected to worsen anxiety symptoms.