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Diagnosis and Management of Anxiety Disorders

REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: This article provides a synopsis of the current understanding of the pathophysiology of anxiety disorders, the biological and environmental risk factors that contribute to their development and maintenance, a review of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) diagnostic criteria, and a practical approach to the treatment of anxiety disorders in adults.

RECENT FINDINGS: Despite the ubiquity of anxiety, the evidence is that most individuals with an anxiety disorder are not identified and do not receive guideline-level care. In part, this may be because of the manifold clinical presentations of anxiety disorders and clinicians' lack of confidence in accurately diagnosing and treating these conditions, especially in nonpsychiatric settings. Anxiety disorders represent the complex interplay between biological, psychological, temperamental, and environmental factors. Converging lines of evidence point to dysfunction in regulating activity in the "threat circuit" in the brain as a putative common pathophysiology underlying anxiety disorders. Evidence-based treatments for anxiety disorders, such as cognitive-behavioral therapy and antidepressant medications, have been shown to regulate activity in this circuit, which consists of reciprocal connections between the dorsomedial prefrontal cortex, insula, and amygdala.

SUMMARY: Anxiety disorders are the most common class of emotional disorders and a leading cause of disability worldwide. A variety of effective treatment strategies are available, which may exert their therapeutic benefits from top-down or bottom-up modulation of the dysfunctional brain activity associated with anxiety disorders.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Giacobbe and Flint discuss the unlabeled/investigational use of D-cycloserine, gabapentin, pregabalin, propranolol, and quetiapine for the treatment of anxiety disorders.

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INTRODUCTION

Fear is a fundamental emotion expressed in all mammals and is necessary for survival. Fear refers to the coordinated emotional, behavioral, and biological response invoked by an immediate threat detected in the environment, allowing organisms to protect themselves through a "fight, freeze, or flight" response. In contrast, anxiety is a future-oriented affective state in which the individual prepares to cope with an uncertain but possible negative event in the absence of a triggering stimulus.

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Although fear and anxiety are separate constructs, they share common neural substrates, as demonstrated by neuroimaging studies.[1] Anxiety responses can be adaptive by orienting the individual toward the detection of a possible threat and coordinating a set of psychological, behavioral, and biological reactions to prepare a response to it. Although the transient experience of anxiety is a core component of the human experience, when this process becomes more context independent, prolonged, excessive, and more difficult to regulate, it can become a pathologic state.

As a group, anxiety disorders are the most common class of disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*). Anxiety disorders are chronic and disabling conditions; they have been estimated to be the sixth leading cause of disability worldwide, surpassing that associated with diabetes mellitus, chronic obstructive pulmonary disease, and osteoarthritis.[2] This article provides a synopsis of the current understanding of the pathophysiology of anxiety disorders, the biological and environmental risk factors that contribute to their development and maintenance, and a practical approach to the diagnosis and treatment of anxiety disorders in adults.

PATHOPHYSIOLOGY AND RISK FACTORS

Anxiety disorders represent the complex interplay between biological, psychological, temperamental, and environmental factors. Recent computational studies of highly anxious people found evidence for processing deficits in decision-making situations that result in an increased propensity to make spurious connections between unrelated events.[3,4] Clinically, this may result in overestimation of risk in situations and inappropriate pairing of neutral stimuli to danger, leading to increased levels of activation of fear-related circuits in the brain and the related behavioral responses seen in the anxiety disorders.[5]

Common neurocircuit abnormalities across the anxiety disorders, as well as disorder-specific dysfunctions, may underlie these observations. Converging lines of evidence have identified that the perception of noxious stimuli elicits activation of a "threat circuit" in the brain, consisting of the reciprocal connections between the dorsomedial prefrontal cortex, insula, and amygdala.[1] Threatening stimuli have been shown to activate this circuit in healthy individuals,[6,7] and increased activation of this circuit is positively correlated to state and trait levels of anxiety in individuals with anxiety disorders.[8] Somatic preoccupation, a common theme across the anxiety disorders, may represent biases in interpreting interoceptive bodily cues as dangerous, thereby leading to excessive cognitive elaboration and inappropriate threat-related processing to benign internal cues, resulting in the trait of anxiety sensitivity. Fonzo and colleagues[9] reported that those with generalized anxiety disorder, social anxiety disorder, and panic disorder share a pattern of greater amygdala activation when processing fearful facial expressions compared to happy facial expressions, which was correlated to levels of anxious traits. Those with panic disorder also uniquely demonstrated increased activation of the insula during this task, consistent with a pattern of hypersensitivity to both external and interoceptive threat cues seen in panic disorder.[9] Based on these data, anxiety disorders can then be characterized by increased vigilance to situations that are perceived as threatening, with concomitant maladaptive and prolonged activation of the threat circuit.

Several factors have been shown to regulate activity in this circuit. The threat circuit has been shown to be inhibited by serotonin. Selective serotonin reuptake

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inhibitors (SSRIs), first-line treatments for a variety of anxiety disorders, have been demonstrated to reduce neurobiological activity in the dorsomedial prefrontal cortex–amygdala circuit to aversive stimuli.[10] The dorsolateral prefrontal cortex is thought to play a key role in emotional regulation through exerting top-down cognitive control on limbic structures, especially via attentional processes.[1] Psychotherapies for anxiety, such as cognitive-behavioral therapy, are felt to exert their effects biologically through enhanced cortical modulation of amygdala activity.[11] Therefore, pathologic anxiety states can be conceptualized as due to excessive bottom-up automatic processing of threat stimuli, impaired top-down attentional control, or both. It is hypothesized that the various evidence-based treatments for anxiety may exert their effects as either dampening bottom-up processing (antidepressant medications) or enhancing top-down control (cognitive-behavioral therapy). Additionally, a variety of genetic and environmental factors have been shown to increase the risk of anxiety disorders, with their effects being mediated, in part, through the excessive activation of the dorsomedial prefrontal cortex–amygdala circuit.[1,8]

Anxiety disorders tend to run in families, with the likelihood of a first-degree relative of an affected proband having an anxiety disorder being 4 to 6 times higher than relatives of unaffected probands.[12] However, it also appears that a general risk for psychopathology is conferred, since children of a parent with an anxiety disorder are at increased risk of developing major depressive disorder[13] or any of the anxiety disorders, not solely the anxiety disorder affecting their parent. Genetic heritability estimates for anxiety disorders have been estimated as 30% to 50%, comparable to those reported for cancer (heritability of 33%; 95% confidence interval, 30% to 37%)[14] and major depressive disorder (heritability of 37%; 95% confidence interval, 31% to 42%),[15] suggesting that both genetics and environmental factors play prominent roles in the genesis of anxiety disorders. Although anxiety disorders are likely to be polygenic, representing the effect of a multitude of genetic variants, each conferring individually small risk effects, one of the most widely studied risk polymorphisms has been 5-hydroxytryptamine (serotonin) transporter gene-linked polymorphic region (5-HTTLPR) in the serotonin-transporter gene promoter. Individuals who are homozygous or heterozygous for the short allele of 5-HTTLPR have increased amygdala reactivity to emotional and threatening stimuli,[16] predisposing them to the development of anxiety and mood disorders. A temperament of behavioral inhibition, characterized by fearfulness, avoidance, and autonomic hyperreactivity in unfamiliar situations, has been linked to an increased lifetime risk of developing an anxiety disorder.[17]

Anxiety disorders typically have their onset in childhood,[18] suggesting that this is an important developmental period for the genesis of anxiety disorders. Indeed, childhood adversities such as abuse and neglect have been linked to increased vulnerability to the development of anxiety disorders. Some studies have found that extreme forms of adversity are associated with alterations in the neurocircuitry involved in fear and emotional processing. Children who experienced institutionalization in an orphanage exhibited elevated reactivity in the amygdala to faces,[19] more typical of adultlike patterns of brain activation, than children who did not experience childhood adversity.[20] These findings may indicate that early adverse experiences in childhood may alter the developmental trajectory of the nascent emotion regulation circuits, thereby enhancing the biological reaction to fearful stimuli and impairing the fear extinction system in

KEY POINTS

- Anxiety disorders are the most common class of emotional disorders and an important cause of disability worldwide.
- The prefrontal cortex, insula, and amygdala are key structures in the pathophysiology of anxiety.
- Reduction in the activation of the prefrontal cortex–amygdala circuit to aversive stimuli may be a common neurobiological mechanism underlying effective treatments for anxiety.
- First-degree relatives of those with anxiety disorders have an increased risk of developing any anxiety disorder or major depressive disorder.
- Anxiety disorders are polygenic, with estimated genetic heritability estimates of between 30% and 50%.
- Most anxiety disorders have their onset in childhood, and cases of atypical "late-onset" anxiety should be considered as due to medical, substance, or mood disorder factors until proven otherwise.

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KEY POINTS

- Environmental factors involving danger or threat, such as abuse or parental loss, increase the risk of developing an anxiety disorder later in life.
- Females are twice as likely to manifest anxiety disorders compared to males.

the brain. Parental factors associated with anxiety disorders in childhood include overprotectiveness; interparental conflict; perfectionism; and modeling of reactions to fearful, stressful, or unpredictable situations.[21]

Stressful life events may play a role in precipitating emotional disorders, with stressors involving loss more typically related to the development of depression, whereas those signaling danger or threat have been specifically associated with the onset of anxiety disorders,[5] perhaps through excessive or maladaptive activation of the threat neurocircuitry. The distal environmental risk factor that has the most profound effect on the development of a subsequent anxiety disorder is childhood sexual abuse, which increases the risk of developing an anxiety disorder by over threefold (odds ratio 3.09; 95% confidence interval, 2.43 to 3.94).[22] Early parental loss through death or separation is associated with an increased risk of subsequent anxiety disorders in offspring, with odds ratios of 1.2 for specific phobia and up to 2.4 for generalized anxiety disorder. A synergistic relationship appears to exist between previous childhood adversity and the impact of current stressful life events, whereby greater childhood adversity produces larger effects of stressful life events on current psychopathology, supportive of a stress-sensitization model.[23] Female gender is a known risk factor for developing an anxiety disorder, with the rate twice as high in females compared to males, although it is not clear if this is caused by biological factors or secondary to the higher rates of stressful life events experienced by women. In summary, it appears likely that both genetic and environmental factors can contribute to the development of anxiety disorders, mediated by inherited and acquired patterns of maladaptive processing of emotional stimuli in the brain.

CLINICAL PRESENTATIONS

This article is confined to the *DSM-5* anxiety disorders: panic disorder, agoraphobia, generalized anxiety disorder, social anxiety disorder, specific phobia, selective mutism, separation anxiety disorder, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition. For information on obsessive-compulsive disorder, refer to the article "Obsessive-Compulsive Disorder" by Peggy M. A. Richter, MD, FRCPC, and Renato T. Ramos, MD,[24] and for information on posttraumatic stress disorder, refer to the article "Assessment and Management of Posttraumatic Stress Disorder" by Janet Ellis, MBBChir, MD, FRCPC, and Ari Zaretsky, MD, FRCPC,[25] in this issue of *Continuum*.

Panic Attacks and Panic Disorder

The *DSM-5* defines a panic attack as a discrete period of intense fear or discomfort that reaches a peak within minutes, during which a number of somatic and cognitive symptoms of anxiety occur (TABLE 12-1).[26] Panic attacks are not specific to panic disorder and can occur in other psychiatric and physical conditions (CASE 12-1). As a result, panic attacks in isolation are not diagnostic. Given the paroxysmal nature of panic attacks and the intensity of the sensations that accompany them, patients experiencing panic attacks seek care from emergency medical services more frequently than patients with major depressive disorder and bipolar disorder.[27] Despite the perception of imminent danger that is experienced during a panic attack, ambulatory monitoring of vital signs has revealed that only modest changes in heart rate (an average increase of 7 beats/min to a heart rate of 90 beats/min) typically occur during these

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DSM-5 Diagnostic Criteria for Panic Disorder[a,b]

TABLE 12-1

A Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feelings of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, light-headed, or faint
9. Chills or heat sensations
10. Paresthesias (numbness or tingling sensations)
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
12. Fear of losing control or "going crazy"
13. Fear of dying

Note: Culture-specific symptoms (eg, tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as one of the four required symptoms.

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

1. Persistent concern or worry about additional panic attacks or their consequences (eg, losing control, having a heart attack, "going crazy")
2. A significant maladaptive change in behavior related to the attacks (eg, behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations)

C The disturbance is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication) or another medical condition (eg, hyperthyroidism, cardiopulmonary disorders)

D The disturbance is not better explained by another mental disorder (eg, the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder)

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

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[b] All the features listed must be present to make a diagnosis of panic disorder.

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episodes.[28] Therefore, evidence of abnormal vital signs is not necessary nor pathognomonic for a panic attack. The majority of panic attacks occur during the daytime, but nocturnal panic attacks can occur and are associated with greater resultant distress and functional impairment.[29] For a diagnosis of panic disorder to be made, the individual must experience recurrent and unexpected panic attacks not due to medical conditions or substances that are followed by at least 1 month of persistent concern or worry about additional panic attacks or an increase in maladaptive avoidance behaviors related to the attacks (TABLE 12-1).

The lifetime prevalence of panic disorder worldwide has been estimated to be 2% to 5%.[30] A bimodal distribution in the age at onset has been observed, with peaks of onset in late adolescence and again in the midthirties. Risk factors for panic disorder include female gender, a history of separation anxiety in childhood, a behaviorally inhibited temperament, and a history of sexual or physical abuse. The majority of people with panic disorder report co-occurring stressful life events in the year preceding the onset of their disorder, often with themes of danger or threat (eg, physical assault, news of a medical diagnosis). Most individuals with panic disorder will have comorbid psychiatric conditions, in particular, major depressive disorder, substance misuse, or other anxiety disorders.[31]

CASE 12-1

A 75-year-old woman was referred to a psychiatrist for management of panic attacks. She described a 3-month history of episodes characterized by pounding in the chest, racing heart, sweating, and dizziness that lasted for hours. She had no identified psychological triggers or personal or family history of psychiatric illness. Her medical history was significant for hyperlipidemia, hypertension, and, most recently, hypothyroidism in the past year. She was on a statin, an angiotensin-converting enzyme inhibitor, a diuretic, and thyroid replacement. The only change in her medications had been the addition of the thyroid replacement pill, with the dosage increased twice in the past 6 months. A recent ECG and echocardiogram were normal. Laboratory testing showed a thyroid-stimulating hormone (TSH) level of 0.01, suggesting an excessive dose of thyroid replacement.

COMMENT

This patient's episodes, although resembling panic attacks, were related to thyroid hormone excess. Late-onset anxiety disorders should prompt a search for other psychiatric or medical conditions that may be contributing to, or mimicking, anxiety (eg mood disorders, medical conditions, and the physiologic effects of substance use or medication). Elderly patients who present with panic attacks require a medical workup to rule out a concurrent medical condition. Red flags for a possible medical etiology for panic attacks in the elderly include an absence of a personal and family history of panic disorder; the presence of neurologic symptoms during a panic attack, such as loss of consciousness, loss of bladder or bowel control, or syncope; and somatic symptoms without the psychological symptoms of panic.

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Panic disorder in late life is usually the continuation of an illness that began earlier in life; it is rare for panic disorder to start for the first time in late life. Therefore, it is important to assess the age of onset of panic disorder (and other anxiety disorders) to determine if the onset of the condition is atypical. Late-onset anxiety disorders should prompt a search for other psychiatric or medical conditions that may be contributing to, or mimicking, anxiety (eg, mood disorders, medical conditions, and the physiologic effects of substance use or medication). Elderly patients who present with panic attacks require a medical workup to rule out a concurrent medical condition. Red flags for a possible medical etiology for panic attacks in the elderly include an absence of a personal and family history of panic disorder; the presence of neurologic symptoms during a panic attack, such as loss of consciousness, loss of bladder or bowel control, or syncope; and somatic symptoms without the psychological symptoms of panic.

Both psychological therapies and medications have been shown to be effective for panic disorder. Robust evidence exists for cognitive-behavioral therapy as a first-line option. Interestingly, in studies of cognitive-behavioral therapy compared to medication or the combination of cognitive-behavioral therapy and medication, combination therapy has not emerged to be clearly more efficacious to cognitive-behavioral therapy alone.[32] Most clinical guidelines do not recommend the routine use of cognitive-behavioral therapy together with antidepressant medication because of the lack of demonstrated superiority of this strategy compared to the use of cognitive-behavioral therapy or medication alone.[33] US Food and Drug Administration (FDA)-approved medications for panic disorder include SSRIs (eg, fluoxetine, paroxetine, and sertraline), serotonin norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine XR), and benzodiazepines (eg, alprazolam and clonazepam) (TABLE 12-2). Data from long-term studies suggest that panic disorder has a fluctuating course, with high rates of symptom improvement (75%) but lower rates of complete functional recovery (12%) over a 3-year-period.[34]

KEY POINTS

- Panic attacks typically present as the perception of frightening physical symptoms, such as racing heart, shortness of breath, and sweating, in the presence of normal vital signs and medical investigations.
- A pattern of recurrent and uncued panic attacks is necessary for a diagnosis of panic disorder.
- In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, the presence of panic disorder is no longer required to make a diagnosis of agoraphobia.

Agoraphobia

Agoraphobia was previously designated as a subtype classifier of panic disorder, but *DSM-5* divides agoraphobia and panic disorder into separate diagnostic entities. Agoraphobia is characterized by marked fear or anxiety about actual or anticipated exposure within public spaces that lasts at least 6 months, with the symptoms of fear or anxiety occurring most of the time in more than one setting (TABLE 12-3). As a result, individuals with agoraphobia fear and avoid these situations because of worry about developing paniclike symptoms or the belief that escape might be difficult. Importantly, the feared situations should not be realistically threatening (eg, walking alone in a dangerous part of town). Those patients who meet criteria for both disorders would be diagnosed with panic disorder and agoraphobia.

The lifetime prevalence of agoraphobia has been estimated to be 2%.[30] The relationship between panic disorder and agoraphobia changes across the lifespan. That is, most older persons with agoraphobia do not have a history of panic attacks[35] and develop agoraphobia following the onset of a physical illness or after a traumatic experience, such as a fall.[36] The ability of the clinician to make the diagnostic distinction between panic disorder with comorbid agoraphobia and agoraphobia alone has important implications for management, as no robust evidence exists

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that pharmacotherapy is effective in treating agoraphobia without a history of panic disorder; the treatment of choice in this situation is in vivo exposure.

Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by a pattern of excessive anxiety and worry about multiple themes that lasts 6 months or more, is difficult for the individual to control, and is accompanied by a number of physical symptoms (TABLE 12-4). Clinically, individuals with generalized anxiety disorder exhibit a pattern of excessive worry about minor matters and intolerance of uncertainty, which in experimental paradigms manifests as automatic or unconscious attentional bias toward potentially threatening stimuli in the environment.[37] In addition to worry, *DSM-5* requires the presence of somatic symptoms consistent with hyperarousal (eg, irritability, muscle tension, insomnia, feeling keyed up) and excessive fatigue. An epidemiologic survey found that only approximately one-third of those in the community who met criteria for generalized anxiety

TABLE 12-2

Medications With US Food and Drug Administration–Approved Indications for Anxiety Disorders

Medication	Panic Disorder	Generalized Anxiety Disorder	Social Anxiety Disorder
Selective serotonin reuptake inhibitors (SSRIs)			
Escitalopram		X	
Fluvoxamine XR			X
Fluoxetine	X		
Paroxetine	X	X	X
Paroxetine CR			X
Sertraline	X		X
Serotonin norepinephrine reuptake inhibitors (SNRIs)			
Duloxetine		X	
Venlafaxine XR	X	X	X
Azapirones			
Buspirone		X	
Benzodiazepines			
Alprazolam	X		
Clonazepam	X		

CR = controlled release; XR = extended release.

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disorder had ever sought help specifically for this condition[27]; this may be because, in nonpsychiatric settings, patients with generalized anxiety disorder rarely identify chronic worry as their primary symptom. Rather, patients with generalized anxiety disorder often develop physical symptoms, such as headaches, back pain, insomnia, and gastrointestinal distress, which bring them to seek care in primary care and medical settings.[38]

The lifetime prevalence of generalized anxiety disorder worldwide has been estimated to be 3% to 5%.[30] A trimodal distribution in the age at onset has been observed, with peaks of onset in childhood and early adulthood, followed by a later peak in the fifth and sixth decades of life, perhaps due to the development of chronic health conditions. Identified risk factors for generalized anxiety disorder

DSM-5 Diagnostic Criteria for Agoraphobia[a,b] **TABLE 12-3**

A Marked fear or anxiety about two (or more) of the following five situations:

1 Using public transportation (eg, automobiles, buses, trains, ships, planes)

2 Being in open spaces (eg, parking lots, marketplaces, bridges)

3 Being in enclosed places (eg, shops, theaters, cinemas)

4 Standing in line or being in a crowd

5 Being outside of the home alone

B The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing paniclike symptoms or other incapacitating or embarrassing symptoms (eg, fear of falling in the elderly; fear of incontinence)

C The agoraphobic situations almost always provoke fear or anxiety

D The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety

E The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context

F The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more

G The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

H If another medical condition (eg, inflammatory bowel disease, Parkinson disease) is present, the fear, anxiety, or avoidance is clearly excessive

I The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder—for example, the symptoms are not confined to specific phobia, situational type; do not involve only social situations (as in social anxiety disorder); and are not related exclusively to obsessions (as in obsessive-compulsive disorder), perceived defects or flaws in physical appearance (as in body dysmorphic disorder), reminders of traumatic events (as in posttraumatic stress disorder), or fear of separation (as in separation anxiety disorder).

Note: Agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned.

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include female gender, childhood adversity, and lower socioeconomic status. A high rate of comorbid physical and mental health conditions is seen, and those with generalized anxiety disorder should be screened for substance abuse and mood disorders.[5] Those with co-occurring depression often describe a long-standing history of worry that became more difficult to control following the onset of the mood disorder. The presence of both generalized anxiety disorder and a mood disorder renders both conditions more difficult to treat.

Generalized anxiety disorder is a chronic condition that may require long-term treatment. It is responsive to both psychological treatments and pharmacotherapy, with response rates in the 30% to 50% range for both modalities.[38] Cognitive-behavioral therapy is considered a first-line option. Cognitive-behavioral therapy protocols for generalized anxiety disorder typically involve both remediation of the typical cognitive biases of overestimation of

TABLE 12-4 ***DSM-5* Diagnostic Criteria for Generalized Anxiety Disorder[a,b]**

A **Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)**

B **The individual finds it difficult to control the worry**

C **The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):**

Note: Only one symptom is required in children.

1. Restlessness or feeling keyed up or on edge
2. Being easily fatigued
3. Difficulty concentrating or mind going blank
4. Irritability
5. Muscle tension
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep

D **The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning**

E **The disturbance is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication) or another medical condition (eg, hyperthyroidism)**

F **The disturbance is not better explained by another mental disorder (eg, anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder)**

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danger and underestimation of resiliency factors and relaxation techniques to decrease symptoms of bodily tension. FDA-approved medications for generalized anxiety disorder include SSRIs (escitalopram and paroxetine), SNRIs (duloxetine and venlafaxine XR), and azapirones (buspirone) (TABLE 12-2). Most experts suggest that benzodiazepines may have an adjunctive role when used on a short-term basis (3 to 6 months).[5,33,38] However, this class of medications should be avoided in those with substance abuse. The recommended minimum duration of medication treatment for generalized anxiety disorder is 1 year.

Social Anxiety Disorder

The lifetime prevalence of social anxiety disorder has been estimated to be up to 10% worldwide,[30] with one-third having the performance-only subtype.[39] Approximately two-thirds of individuals with social anxiety disorder are female. The typical age of onset is midadolescence, with de novo emergence in the fourth decade of life and after being very uncommon; such later-onset cases should prompt a search for other comorbid psychiatric, medical, or substance-related etiologies. Only a small minority of patients with social anxiety disorder seek treatment. Data from a community sample of US residents found that less than 10% of people who meet the criteria for social anxiety disorder had ever seen a clinician for social anxiety.[27] Social anxiety disorder is often a chronic condition, with a 5-year recovery rate for those seeking treatment in the range of 25%.[40]

The core feature of social anxiety disorder is fear of negative appraisal by others in social or performance situations (TABLE 12-5 and CASE 12-2). For example, patients with social anxiety disorder may have excessive or unrealistic fear of social or performance situations and intolerance of the possibility of embarrassment or scrutiny by others. Common situations that may be difficult for those with social anxiety disorder include public speaking and attending social functions where there are others who are unknown to the individual. Individuals with social anxiety disorder may overestimate the likelihood of a negative event occurring (eg, "no one will like me at the party"), leading to activation of a threat-related circuit in the brain that can produce a dysphoric physical state (eg, rapid heartbeat, sweaty palms) via an autonomic arousal response mediated by the sympathetic nervous system. Withdrawal from such events where negative appraisal is anticipated will produce a rapid cessation of the negative emotional and physical state, reinforcing the avoidance behavior. Ultimately, through repetition of avoidance behavior, individuals with social anxiety disorder do not provide themselves with opportunities where they can potentially disconfirm their assumptions of having negative social interactions with others, thereby strengthening the fear-avoidance cycle and leading to impaired interpersonal and vocational functioning. Avoidance of a feared social situation can also lead to negative self-appraisal in those with social anxiety disorder, including ruminations about the event and a reinforcing cycle of embarrassment, self-loathing, depression, and further withdrawal. Randomized controlled trials have shown strong evidence for the efficacy of cognitive-behavioral therapy and short-term psychodynamic therapy in the treatment of social anxiety disorder.[39] FDA-approved medications for social anxiety disorder include the SSRIs fluvoxamine XR, paroxetine, paroxetine CR, and sertraline and the SNRI venlafaxine XR (TABLE 12-2). If fear or anxiety is restricted to

KEY POINTS

- Generalized anxiety disorder is associated with high rates of comorbid conditions, such as physical health issues, substance abuse, and mood disorders.
- Social anxiety disorder is a chronic condition associated with fear of negative appraisal by others, excessive or unrealistic fear of social or performance situations, and intolerance of the possibility of embarrassment or scrutiny by others in social situations.

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speaking or performing in public, the performance anxiety only subtype would apply. Evidence exists for the off-label use of beta-blockers for performance anxiety.

Specific Phobia

The cross-national lifetime prevalence of specific phobia has been estimated to be 7.4%.[43] Natural environment phobias (eg, fear of bodies of water or heights) are the most common subtype, followed by situational phobias (eg, flying), animal phobias (eg, spiders or dogs), and blood-injury phobias (eg, fear of needles). In contrast to other anxiety disorders, the blood-injury subtype of specific phobia involves decreased rather than increased sympathetic nervous system activity, leading to syncope and vasovagal-type reactions.[44] Approximately 75% of cases of specific phobia will have their onset within the first decade of life.[45] Having multiple specific phobias is the rule rather

TABLE 12-5 ***DSM-5* Diagnostic Criteria for Social Anxiety Disorder**[a–c]

A **Marked fear or anxiety related to one or more social situations in which the individual is exposed to scrutiny by others. Examples include social interactions (eg, having a conversation, meeting unfamiliar people), being observed (eg, eating or drinking), and performing in front of others (eg, giving a speech).**

Note: In children, the anxiety must occur in peer setting and not just during interactions with adults.

B **The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (ie, will be humiliating or embarrassing; will lead to rejection or offend others).**

C **The social situations almost always provoke fear or anxiety.**

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D **The social situations are avoided or endured with intense fear or anxiety.**

E **The fear or anxiety is out of proportion to the actual threat posed by the social situation and to sociocultural context.**

F **The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.**

G **The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.**

H **The fear, anxiety, or avoidance is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication) or another medical condition.**

I **The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder).**

J **If another medical condition (eg, Parkinson disease, obesity, disfigurement from burns or injury), is present, the fear, anxiety, or avoidance is clearly unrelated or is excessive.**

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

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[b] If fear or anxiety is restricted to speaking or performing in public, social anxiety disorder should be specified as performance anxiety only.

[c] All the features listed must be present to make a diagnosis of social anxiety disorder.

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than the exception, with most patients with specific phobia having three or more sources of phobias in their lifetime. Similar to most anxiety disorders, approximately two-thirds of individuals with specific phobia are female. Specific phobias can be transient in childhood, with some affected individuals growing out of their fears through the processes of developmental maturation and naturalistic exposure to fearful stimuli over time. However, in other cases, specific phobias are chronic, persisting into and throughout the adult years.[46]

CASE 12-2

A 21-year-old woman presented with a history of anxiety in social situations dating back to adolescence, which resulted in her feeling negatively appraised by others in her college classes when doing group assignments. She was reluctant to speak in class, but when she did, her comments were valued by others. She recognized that the anxiety was out of proportion to the actual threat of the situations. She had no other psychiatric, medical, or substance-use problems.

Social anxiety disorder was diagnosed. The severity of her symptoms was deemed to be mild based on her score of 8 on the Generalized Anxiety Disorder 7-Item Scale (GAD-7) self-report questionnaire.[41] She was provided with reassurance and education about the nature of anxiety and recommended to engage in healthy coping strategies, such as aerobic exercise, relaxation, and mindfulness techniques, and to avoid excessive use of caffeine and other substances. She was also provided with information about online educational resources on anxiety disorders, and a follow-up appointment was arranged for 1 month later.

At the follow-up appointment, she reported that the symptoms of social anxiety had worsened, and she was missing half of her classes and avoiding some friends. Her GAD-7 score was now 14. She reported following the advice and accessing the resources that had been provided at her last visit. She asked about what to do next, and psychotherapy and medication options were discussed.

COMMENT

A stepped-care approach to the selection of treatment modalities for anxiety disorders has been advocated based on symptom severity.[42] Quantification of the severity of anxiety symptoms can be aided by the use of patient-rated questionnaires. The GAD-7 is a validated seven-item self-report measure applicable to multiple anxiety disorders.[41] Scores in the range of 5 to 9 are consistent with mild anxiety, 10 to 14 with moderate anxiety, and 15 or more with severe anxiety. For mild anxiety, the treatment recommendation is for psychoeducation, support, and watchful waiting. Cognitive-behavioral therapy (including Internet- or computer-based cognitive-behavioral therapy), pharmacotherapy, or both, is recommended for those with moderate anxiety. Severe or treatment-resistant anxiety symptoms warrant cognitive-behavioral therapy concurrently with pharmacotherapy.[42]

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The primary treatment approach for specific phobia is psychological treatment, such as cognitive-behavioral therapy and exposure-based therapies. No medications are FDA approved for specific phobia, although off-label use of benzodiazepines for short-term anxiolysis when the individual is unavoidably faced with confronting the phobic situation (eg, flying) or the beta-blocker propranolol for performance anxiety is not uncommon.

Selective Mutism

Selective mutism is characterized by an individual's failure to speak in certain social situations, with the presence of normal ability to speak in other settings. The prevalence rates of selective mutism have been estimated to range from 0.11% to 2.2% in children, with an average age of onset of 2 to 5 years. The most common presentation is failure to speak in school, resulting in significant adaptation difficulties in social and academic spheres.[47]

Identified risk factors for selective mutism include a temperament of behavioral inhibition, communication delays, bilingualism, immigration, and a history of parental social anxiety disorder or selective mutism. Although the majority of children with selective mutism have a complete remission of their symptoms in adolescence, rates of mood and anxiety disorders are high in adulthood, with 58% having a psychiatric disorder, most commonly social anxiety disorder.[48]

Treatment approaches consist of psychoeducation, cognitive-behavioral therapy, and graduated exposure to situations requiring verbal communication. No medications are FDA approved for selective mutism; limited literature exists for the use of SSRIs.[49]

Separation Anxiety Disorder

Separation anxiety disorder is characterized by excessive fear or anxiety regarding separation from attachment figures that is developmentally inappropriate and present for at least 4 weeks in a child or adolescent and for at least 6 months in an adult. Separation anxiety disorder is a new addition to the group of anxiety disorders in *DSM-5*. Changes to the diagnostic criteria for separation anxiety disorder no longer require an onset of symptoms before the age of 18 years. Typical presentations in adulthood may include fears that their attachment figure, such as a spouse or child, will come to harm, resulting in extreme efforts to remain in close contact with them.[50] The prevalence of separation anxiety disorder in adults has been estimated to be 4.8% worldwide, with adult onset in 43.1% of cases.[51]

Identified risk factors for separation anxiety disorder include female gender, childhood parental loss, and lifetime trauma. The presence of separation anxiety disorder is generally associated with a worse prognosis for mood and other anxiety disorders when those disorders are comorbid with separation anxiety disorder.[52] Childhood onset of separation anxiety disorder has been linked to an increased risk specifically for panic disorder in adulthood, and these two conditions may share a common neurobiology as evidenced by hypersensitivity to symptom provocation with a 35% carbon dioxide challenge.[53] Treatment approaches consist primarily of psychological treatments, including cognitive-behavioral therapy and psychodynamic-informed approaches.[52] No medications are FDA approved for separation anxiety disorder, although SSRIs

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have been used given the symptom overlap of separation anxiety disorder with other anxiety disorders.

MANAGEMENT OF ANXIETY DISORDERS

A variety of effective treatment strategies for anxiety are available, including both psychosocial and biological interventions. The following section provides a proposed general clinical approach to the evaluation and treatment of anxiety disorders, augmenting the management discussions in the previous sections about the specific forms of anxiety disorders.

General Approach to Evaluating Anxiety

The most important step in the treatment of anxiety is to establish the cause, triggers, and duration of the symptoms. This is achieved through the exploration of the nature of the symptoms (eg, worries, somatic symptoms, and avoidance behaviors), proximal triggers for the anxiety (eg, stressful life events, medical illnesses, substance abuse, and change in medications), and the patient's thoughts and beliefs regarding his or her anxiety. For example, anxiety and avoidance about attending a social engagement may be due to low mood and a lack of interest (major depressive disorder) or due to the fear of being negatively scrutinized by others (social anxiety disorder), of having panic attacks (panic disorder and agoraphobia), of being separated from a loved one (separation anxiety disorder), of the need to travel via airplane (specific phobia), or of the need to give a speech (social anxiety disorder, performance subtype), to name a few possible causes. Short-term anxiety can be treated symptomatically with support, reassurance, and, if needed, a time-limited course of a benzodiazepine.

Given that anxiety disorders are diagnoses of exclusion, it is important to rule out the contribution of concurrent medical illnesses and medications. A symptom-targeted physical examination should be performed to rule out an underlying medical condition. Factors increasing the possibility of a medical or substance etiology for an anxiety disorder include no previous history of an anxiety disorder; an onset of an anxiety disorder later in the lifespan than the usual natural history; a recent change in medical health, prescribed medication, or substance use pattern; and the presence of atypical symptoms, such as loss of consciousness, loss of bladder or bowel control, or syncope during a presumed panic attack. Recommended screening investigations for those presenting with de novo anxiety symptoms or an exacerbation of an existing anxiety condition may include a complete blood count, electrolytes, fasting glucose, thyroid-stimulating hormone (TSH), urine toxicology for substance use, and an ECG.[5,33] Further investigations and a more focused physical examination are dictated by the presentation.

Clinical experience and guidelines support that anxiety disorders can be treated with either psychotherapy or pharmacotherapy,[5,33,42] with short-term response rates up to 50% to 60% with either approach. Often, the choice of treatment depends on patient preference, the availability of treatments, and clinical factors. A stepped-care approach to the selection of treatment modalities for anxiety disorders has been advocated based on symptom severity.[42] Quantification of the severity of anxiety symptoms can be aided by the use of patient-rated questionnaires. Studies have validated the psychometric properties of the Generalized Anxiety Disorder 7-Item Scale (GAD-7), a self-report measure applicable to multiple anxiety disorders in primary care and medical settings.[41]

KEY POINTS

- Phobias in childhood may be transient, but those that persist into adulthood will typically remain chronic.
- Separation anxiety disorder, which is characterized by excessive fear or anxiety regarding separation from attachment figures, has pathophysiologic links to panic disorder and is a new addition to the group of anxiety disorders in *DSM-5*.
- The most important step in the treatment of anxiety is the establishment of the diagnosis, which includes an exploration of the nature of the symptoms and an assessment of comorbid medical and psychiatric factors such as mood disorders, suicidality, and substance use.
- Anxiety disorders are chronic but treatable conditions.
- Selection of the appropriate treatment modality for anxiety disorders may, in part, be guided by symptom severity and by patient-rated questionnaires, such as the Generalized Anxiety Disorder 7-Item Scale.

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KEY POINTS

- Education about the nature of anxiety disorders, avoidance of known exacerbating factors, the promotion of healthy coping strategies, and emotional support should be provided to all patients.
- A stepped-care approach for those with moderate or severe anxiety has been recommended.
- The routine coadministration of psychotherapy and medications has not been shown to be superior to either approach alone.
- Robust data exist to support cognitive-behavioral therapy in the treatment of anxiety disorders, whether administered directly by a therapist or via the Internet.

The GAD-7 is a seven-item questionnaire with total scores ranging from 0 to 21. A total score in the range of 5 to 9 is consistent with mild anxiety, 10 to 14 with moderate anxiety, and 15 or more with severe anxiety. For those with mild anxiety, the treatment recommendation is for psychoeducation, support, and watchful waiting; if symptoms worsen, cognitive-behavioral therapy may be added (including Internet- or computer-based cognitive-behavioral therapy). Cognitive-behavioral therapy, pharmacotherapy, or both are recommended for those with moderate anxiety. Severe or treatment-resistant anxiety symptoms warrant cognitive-behavioral therapy concurrently with pharmacotherapy.[42]

Treatment Approach for Mild Symptoms

Patients and their families should be given education about the nature of anxiety, including both psychological and physical symptoms; the known clinical course of the specific anxiety disorder(s) affecting them; and the treatment options available. Clinical experience suggests that patients greatly benefit from discussions emphasizing the common frequency of anxiety conditions, the biological and genetic component of anxiety, and the good recovery rates with treatment. Patients should also be educated to avoid possible common exacerbating factors for anxiety, such as excessive use of caffeine or alcohol, and to potentially reduce medications with stimulating properties. Medications and substances with sedating effects, such as alcohol or marijuana, may be commonly used by people to try to alleviate anxiety; however, they can potentially precipitate panic and anxiety in the withdrawal phase (CASE 12-3). Patients should be encouraged to get regular aerobic exercise and to practice relaxation techniques.

Treatment Approach for Moderate Symptoms

The stepped-care approach to anxiety disorder recommends cognitive-behavioral therapy, pharmacotherapy, or both for those with moderate anxiety.[42] Currently, biomarker data to predict preferential response to psychotherapy or medications is lacking, although neuroimaging data suggest that similar neurobiological correlates to response are seen for both modalities.[54] In long-term studies, administering cognitive-behavioral therapy and an SSRI together has not routinely been found to be superior to cognitive-behavioral therapy alone,[33,55] although this combination may have a role to play in those with severe or treatment-resistant anxiety.[5] Before initiating treatment, patients should be made aware that anxiety may worsen in the early stages of treatment with antidepressant medication as well as in psychotherapy when individuals begin to confront fear-provoking stimuli and attempt to alter their pattern of phobic avoidance.

PSYCHOTHERAPY. Cognitive-behavioral therapy is a type of psychotherapy that attempts to change the thoughts and behaviors that are fundamental to maintaining the anxiety disorder. Given the evidence that people with anxiety disorders tend to overestimate the risk of a situation and underestimate their ability to manage the risk, the goals of cognitive-behavioral therapy include identifying and challenging cognitive biases that contribute to this misappraisal and minimizing avoidant behavior that perpetuates the anxiety. This is accomplished through a time-limited collaborative relationship between patient and therapist that is focused on problem solving. The efficacy of

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cognitive-behavioral therapy in the treatment of anxiety disorders is well established, and it is considered a first-line therapy for anxiety disorders.[5,33,38,39] A 2016 meta-analysis found large to very large treatment effect sizes associated with cognitive-behavioral therapy, with numbers needed to treat of 1.42, 2.54. and 2.54 for panic disorder, generalized anxiety disorder, and social anxiety disorder, respectively.[56]

Components of cognitive-behavioral therapy interventions include cognitive restructuring through the evaluation of automatic thoughts and the provision of homework assignments that provide patients the opportunity for experiential learning to modify the nature of their beliefs regarding anxiety triggers.

CASE 12-3

A 43-year-old man presented to the emergency department reporting symptoms of sudden-onset chest tightness, dyspnea, sweating, and anxiety. The symptoms occurred while the patient was sitting in his backyard reading. He reported a long-standing history of such episodes over the past 15 years, which occurred both when he was under extreme stress and unprovoked. He described using increasing amounts of alcohol over the past year to manage his sense of anxiety and worry about another episode occurring. In a typical week, he consumed more than 20 alcoholic drinks. He had no signs or symptoms of acute alcohol intoxication or withdrawal or other comorbid medical or psychiatric issues.

His vital signs were normal, and general physical and neurologic examinations were normal. Laboratory investigations were normal, including troponins, and ECG and other investigations were normal. Urine toxicology was positive only for alcohol. He was diagnosed with panic disorder and alcohol dependence and provided with psychoeducation about the nature of anxiety and the role that his alcohol use may have played in perpetuating his anxiety difficulties. He was also provided with information on relaxation techniques and given a referral to psychiatric urgent care to be seen the following week. He was relieved to hear that he was not having a heart attack but asked if he could receive a prescription for a medication to help his anxiety in the future.

COMMENT

In patients who present with anxiety disorders, it is essential to assess for the presence of alcohol and substance abuse. Benzodiazepines should be avoided in patients with a history of substance abuse because of the potential for dependence and the ability of benzodiazepines to potentiate the effects of alcohol and opioids, which can increase the likelihood of death in overdose. In cases where pharmacologic interventions are deemed necessary, priority should be given to selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and buspirone, although it may take weeks to months to see the full effects of these medications. Pregabalin, a medication that does not bind to benzodiazepine receptors and has reduced addiction potential, was given to provide more immediate anxiolysis given this patient's history of substance abuse.

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Graduated exposure to fearful stimuli involves helping patients to systematically confront feared but otherwise safe stimuli in a manner that promotes extinction of the feared stimuli through corrective learning experiences. Other common elements of cognitive-behavioral therapy for anxiety include relaxation and breathing techniques to decrease physiologic arousal. Psychological therapies are the mainstay of treatment for specific phobia, agoraphobia, separation anxiety disorder, and selective mutism.

A number of anxiety disorder–specific cognitive-behavioral therapy protocols have been developed based on the presumptive core cognitive components of each disorder. A 2017 randomized controlled trial aimed to elucidate the active elements of cognitive-behavioral therapy for anxiety disorders.[57] Patients were randomly assigned to receive either a disorder-specific cognitive-behavioral therapy protocol or a transdiagnostic unified protocol for all anxiety disorders, which prioritized the reactions to the emotional experience, such as autonomic arousal, rather than its situational precipitants. The transdiagnostic unified protocol consisted of five core treatment modules: (1) mindful emotion awareness, (2) cognitive flexibility, (3) identifying and preventing patterns of emotion avoidance, (4) increasing awareness and tolerance of emotion-related physical sensations, and (5) interoceptive and situational emotion-focused exposures. While the disorder-specific and transdiagnostic protocols each produced reductions in anxiety compared to wait-list controls, with large effect sizes for improvement, those who were randomly assigned to the transdiagnostic protocol were more likely to complete treatment.[57] Therefore, it appears that a focus on the common emotional experiences across the anxiety disorders is effective in treating anxiety disorders.

Although the evidence base for cognitive-behavioral therapy in anxiety disorders is strong, the majority of persons with an anxiety disorder do not receive this treatment, despite patients' preference for psychotherapy rather than pharmacotherapy.[58] Data from a community-based survey revealed that only 1 in 10 people with social anxiety disorder, 1 in 3 people with a diagnosis of generalized anxiety disorder, and just under 1 in 2 with panic disorder had ever seen a therapist or doctor for their condition.[27] Barriers include the limited number of available therapists trained in cognitive-behavioral therapy, the time and costs associated with the treatment, and stigma or fear of self-disclosure to another person.[59] These constraints have prompted investigation of alternative means of delivering cognitive-behavioral therapy, including Internet-based cognitive-behavioral therapy. Randomized controlled trials have demonstrated that Internet-based cognitive-behavioral therapy is equally effective as face-to-face cognitive-behavioral therapy for social anxiety disorder, panic disorder, and generalized anxiety disorder, with durable effects lasting months after completion.[60] Therefore, Internet-based cognitive-behavioral therapy may be an important option for people who experience difficulties traveling to appointments with a therapist because of the fear and avoidance inherent in anxiety disorders. Mindfulness meditation has been found to regulate anxiety states, with reductions in anxiety associated with increased activation of the anterior cingulate cortex, ventromedial prefrontal cortex, and anterior insula following this treatment.[61] For social anxiety disorder, evidence exists from randomized trials for manual-based short-term psychodynamic therapy with short- and long-term results comparable to cognitive-behavioral therapy and superior to wait-list controls.[39,62]

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Other types of psychotherapy have also been used to treat anxiety disorders, but, in general, the support for these therapies is based on fewer or lower-quality studies.

MEDICATIONS. Four classes of medications have received FDA approval for the treatment of anxiety disorders: SSRIs, SNRIs, azapirones, and benzodiazepines. Multiple meta-analyses and clinical guidelines recommend either SSRIs or SNRIs as a first-line choice for the treatment of anxiety disorders.[33,55] FDA-approved medications are listed in TABLE 12-2. It is important to note that evidence exists for the efficacy of SSRIs and SNRIs beyond those with an FDA indication for an anxiety disorder,[33] suggesting that this may be a class effect rather than restricted to certain compounds. The effective dosages of these medications are similar to those used for major depressive disorder (TABLE 12-6 [63–66]). Because patients with anxiety may have increased sensitivity to medication side effects or misattribute physical symptoms of anxiety to the medication, it is recommended to start at a low dosage and slowly increase the dosage every 2 to 4 weeks, as tolerated, to achieve dosages in the therapeutic range.

SELECTING A MEDICATION. In the absence of biomarkers to guide decision making, several factors may aid clinicians in choosing a medication and longitudinally monitoring its effects. The first is the specific diagnosis. As previously noted, several anxiety disorders respond to antidepressants. In contrast, buspirone is limited to the treatment of generalized anxiety disorder. Buspirone, an azapirone with no effects on γ-aminobutyric acid (GABA), works as a 5-hydroxytryptamine 1A (5-HT_{1A}) partial agonist. Similar to an antidepressant, buspirone takes 3 to 4 weeks to start exerting its effects and may have a limited role in treating acute anxiety. The efficacy of beta-blockers, such as propranolol, appears to be restricted to those with the performance subtype of social anxiety disorder. Propranolol is effective in doses between 20 mg and 40 mg when taken 30 minutes before a predictable performance-related anxiety, such as giving a presentation. This medication may be preferentially effective in minimizing peripheral manifestations of anxiety, such as tremor. Heart block, chronic obstructive pulmonary disease, asthma, and bronchospasm are considered contraindications to propranolol, and monitoring of vital signs is essential when using this medication.

Assessing for comorbid depressive symptoms may also help in choosing a medication. Given that little evidence exists for the antidepressant properties of benzodiazepines, those with anxiety and major depressive disorder should be treated with an SSRI or SNRI. Since response rates seen across the different antidepressants are deemed to be roughly equivalent, the selection of an antidepressant medication may, in part, be based on its side effect profile, understanding that both efficacy and acceptability ultimately contribute to its clinical effectiveness (TABLE 12-7). Common side effects of SSRIs include gastrointestinal upset, sedation, insomnia, and sexual dysfunction. The presence of certain side effects, such as erectile dysfunction, may be deal breakers for some, but not all, patients. It is important to discuss potential side effects with patients before starting a medication to determine if they would prove to be barriers to adherence. Paroxetine has more anticholinergic activity than other SSRIs. Anticholinergic effects can cause cognitive impairment, especially in older individuals and those with preexisting brain disease. The tertiary amine tricyclic

KEY POINTS

- US Food and Drug Administration–approved medications for the treatment of anxiety disorders are from four pharmacologic classes: selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, azapirones, and benzodiazepines.
- To minimize the risk of premature discontinuation of medication, start at a low dose and slowly increase the dose every 2 to 4 weeks up to the therapeutic range.
- The azapirone medication buspirone has antianxiety effects limited to reduction of worry. As such, it has limited effects for other indications beyond generalized anxiety disorder, although it may be a helpful option when the use of a benzodiazepine is contraindicated.
- The beta-blocker propranolol may be effective for peripheral manifestations of anxiety (eg, tremor) in those with the performance subtype of social anxiety disorder.

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TABLE 12-6 **Commonly Prescribed Medications for Anxiety Disorders**

Class/Medication	Initial Total Daily Dosage (mg)	Target Total Daily Dosage (mg)[a]	Frequency of Use	Common Side Effects
Selective serotonin reuptake inhibitors (SSRIs)[b]				
Citalopram[c]	10	20–40	Daily	Nausea, somnolence, insomnia, sexual dysfunction, loose stools, sweating, headache
Escitalopram[c,d]	5	10–20	Daily	
Fluvoxamine XR[d]	50	100–300	Daily	
Fluoxetine[d]	5–10	20–80	Daily	
Paroxetine[d]	10	20–60	Daily	
Paroxetine CR[d]	12.5	25–75	Daily	
Sertraline[d]	25	50–200	Daily	
Serotonin norepinephrine reuptake inhibitors (SNRIs)[b]				
Duloxetine[d]	30	60–90	Daily in the morning	SSRI side effects, hypertension
Venlafaxine XR[d]	37.5	75–225	Daily in the morning	
Azapirones				
Buspirone[d]	10	20–60	Daily	Dizziness, nausea, insomnia, headache
Benzodiazepines				
Alprazolam[d]	0.5–1.0	2–6	3 times a day	Sedation, psychomotor impairment, dependence, tolerance
Clonazepam[d]	0.25–0.50	1–2	Daily or 2 times a day	
Diazepam	2.5–5.0	10–40	Daily	
Lorazepam	0.5–1.0	1–4	2 times a day	
Other				
Gabapentin	100–200	100–1800	2 or 3 times a day	Sedation
Pregabalin	150	150–600	2 or 3 times a day	Sedation, weight gain, peripheral edema
Propranolol	10	10–40	As needed 30–60 minutes before situation	Bradycardia, hypotension
Quetiapine	25	50–200	Daily at bedtime	Sedation, weight gain, metabolic effects

[a] Lower dosages are recommended for the elderly.

[b] Evidence exists for the efficacy of SSRIs and SNRIs beyond those with a US Food and Drug Administration (FDA) indication for an anxiety disorder, suggesting that this may be a class effect rather than restricted to certain compounds.

[c] A warning exists of increased risk of the QT prolongation at doses of citalopram greater than 40 mg (greater than 20 mg in those older than 60 years of age) and escitalopram greater than 20 mg. In those age 65 years and older, the maximum recommended dose of citalopram is 20 mg/d[63] and the maximum recommended dose of escitalopram is 10 mg/d[64] (Health Canada). The FDA recommends a maximum dose of 20 mg/d for citalopram in those older than age 60.[65] For escitalopram, the maximum recommended dose is 10 mg/d in the elderly.[66]

[d] FDA indication for an anxiety disorder.

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antidepressants have been found to be effective in treating anxiety but are generally not recommended as a first- or second-line choice because of their potential for causing orthostatic hypotension, cardiotoxicity, and anticholinergic side effects. First-generation monamine oxidase inhibitors (MAOIs), such as phenelzine, also are not considered first-line therapies for the treatment of anxiety disorders because of their potential for orthostatic hypotension and peripheral edema and the need to avoid tyramine-containing foods and certain medications to prevent development of a hypertensive crisis.

When choosing a medication, it is important to assess the patient for suicidality. In a systematic review and meta-analysis, anxiety disorders apart from obsessive-compulsive disorder were associated with an increased risk of suicidal thoughts (odds ratio 2.89; 95% confidence interval, 2.09 to 4.00), attempted suicides (odds ratio 2.47; 95% confidence interval, 1.96 to 3.10), and completed suicides (odds ratio 3.34; 95% confidence interval, 2.13 to 5.25).[67] In patients with an anxiety disorder, a comorbid mood disorder may have a synergistic effect, as the risk of suicidal behavior in this group appears to be greater than in those with either an anxiety or mood disorder alone, perhaps because of anxiety facilitating the transition from suicidal thoughts to behaviors.[68] In those with anxiety and suicidality, caution should be exerted to provide smaller quantities of medication to minimize the risk of a fatal overdose. More frequent appointments to assess the effects of treatment and safety are prudent.

It is also important to assess for alcohol and substance abuse when selecting a medication. Because of the potential for dependence and the ability to potentiate the effects of alcohol and opioids, benzodiazepines should be avoided in patients with a history of substance abuse. Although concerns exist about the increased

Rates of Side Effects of US Food and Drug Administration–Approved Antidepressants for Anxiety Disorders[a] TABLE 12-7

Class/ Medication	Constipation	Diarrhea	Dry Mouth	Fatigue	Headache	Insomnia	Nausea	Sedation	Sexual Dysfunction
Selective serotonin reuptake inhibitors (SSRIs)									
Escitalopram	0–9%	0–9%	0–9%	0–9%	0–9%	0–9%	10–29%	0–9%	10–29%
Fluvoxamine	10–29%	0–9%	10–29%	0–9%	>30%	10–29%	>30%	>30%	>30%
Fluoxetine	0–9%	0–9%	10–29%	0–9%	0–9%	10–29%	10–29%	10–29%	10–29%
Paroxetine	10–29%	10–29%	10–29%	0–9%	10–29%	10–29%	10–29%	10–29%	>30%
Sertraline	0–9%	10–29%	10–29%	10–29%	>30%	10–29%	>30%	10–29%	>30%
Serotonin norepinephrine reuptake inhibitors (SNRIs)									
Duloxetine	10–29%	0–9%	10–29%	0–9%	0–9%	10–29%	>30%	0–9%	10–29%
Venlafaxine	10–29%	0–9%	10–29%	0–9%	10–29%	10–29%	>30%	10–29%	10–29%

[a] Based on unadjusted rates from product monographs.

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use of benzodiazepines in recent years,[69] they continue to have a role in selected patients with anxiety without substance abuse when used judiciously. Long-term use of benzodiazepines has been shown to increase with age, with 14.7% of those between 18 and 35 years of age receiving a prescription for benzodiazepines in the United States during the year, compared to 31.4% of those 65 to 80 years of age.[69] Despite the increased use of this class of medications in the elderly, benzodiazepines should be used with caution in this age group because of concerns about falls, sedation, and cognitive impairment. Strategies to decrease the likelihood of long-term benzodiazepine use and dependence include the use of shorter-acting benzodiazepines in small supplies and with frequent reassessment of the ongoing need for them.[70]

Approach to Severe Anxiety Disorders or Treatment Nonresponse

Anxiety disorders are considered chronic conditions with relapsing-remitting courses. Several factors have been associated with treatment resistance, including illness characteristics (younger age of onset, longer course of illness, greater severity and frequency of symptoms, persistent anticipatory anxiety and avoidance, substance abuse, a history of childhood abuse, a family history of psychiatric disorders, and psychiatric and medical comorbidities), sociodemographic factors (male sex, low socioeconomic status, poor social supports), and possible biological factors (S allele of 5-HTTLPR, lower serum brain-derived neurotrophic factor [BDNF] level).[71]

In cases of an incomplete response, an important initial step is to determine if the lack of response is because of medication factors such as inadequate dose and duration of treatment. Pseudoresistance factors include nonadherence to treatment and inaccurate or concurrent diagnoses. A review of the literature estimated that approximately half of patients with an anxiety disorder prematurely discontinue their treatment sessions, and this may reach up to 85% of those with social phobia.[72] Group therapies are more likely to be declined than individual therapy.[73] Rates of nonadherence to prescribed medications are similar. In an analysis of a large managed care database, Stein and colleagues[74] estimated that 57% of patients diagnosed with an anxiety disorder had discontinued their SSRI or SNRI medication at 6 months. Illness comorbidity has not been consistently identified as contributing to nonadherence in anxiety disorders, and, in fact, investigators have proposed a bimodal relationship with higher rates of premature discontinuation of treatment in those at the mildest and most severe ends of the severity perspective because of lack of investment in ongoing treatment and extreme functional impairment, respectively.[75] Given that fear and avoidance are key components in the genesis and perpetuation of anxiety disorders, it is prudent to explore patients' beliefs regarding illness and the proposed treatments.

Nonresponse to an initial course of cognitive-behavioral therapy or medication should also prompt a reexamination of the diagnosis to explore whether factors such as latent substance abuse or mood disorder may be contributory. Following the confirmation of an accurate diagnosis and lack of nonadherence to treatment, the next step is to determine whether a therapeutic dose of treatment has been obtained. Typical medication dose ranges are shown in TABLE 12-6. The following step is to determine whether the dose of treatment has been in place for an adequate duration of time. It is recommended that a trial of an antidepressant should be for a minimum of 8 to 10 weeks, including 2 weeks

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or more at the highest tolerated dose. If effective, the antidepressant should be maintained at the highest tolerated dose for 9 to 12 months to minimize the risk of relapse.[5] A typical course of cognitive-behavioral therapy would be 12 to 16 sessions.

A lack of consensus exists regarding the definitive next steps following a lack of response to an adequate trial of treatment.[33,76] Options include switching from one first-line treatment modality to the other (ie, from cognitive-behavioral therapy to antidepressant medication or vice versa). For those who have failed a trial of an SSRI, it has been suggested that an alternative SSRI be tried.[42] If the patient still has no response, switching to an SNRI, such as duloxetine or venlafaxine, has been recommended. An alternative option is to combine cognitive-behavioral therapy and antidepressant medication. A third option is to augment psychotherapy or pharmacotherapy with other strategies not felt to have strong anxiolytic properties on their own.

The paucity of evidence-based treatments has led investigators to explore the efficacy of novel strategies for those with difficult-to-treat anxiety disorders. Medication strategies for treatment-resistant generalized anxiety disorder or for when a benzodiazepine should be avoided include pregabalin and buspirone. Pregabalin, an established treatment for fibromyalgia, epilepsy, and neuropathic pain, has efficacy in generalized anxiety disorder.[5] Pharmacologically, pregabalin is a GABA analogue that does not bind to benzodiazepine receptors; it has clinically demonstrated anxiolytic effects, with a decreased risk of dependence. Given that both pregabalin and buspirone do not bind to benzodiazepine receptors, both compounds have reduced addiction potential and may be preferred treatments for those with a history of alcohol abuse. However, prescribers of pregabalin (and gabapentin) should pay attention to signs of abuse, especially in those patients with a history of substance use disorders. Limited evidence exists for the efficacy of atypical antipsychotics, such as quetiapine, in panic disorder or generalized anxiety disorder.[76] When augmentation with an atypical antipsychotic is used, the potential risks of weight gain, extrapyramidal symptoms, and metabolic syndrome should be actively monitored in patients. Another putative augmentation strategy for anxiety is D-cycloserine, an antibiotic traditionally used to treat tuberculosis. D-Cycloserine acts as a partial *N*-methyl-D-aspartate (NMDA) agonist in the brain. Preclinical studies have indicated that D-cycloserine is able to enhance the resolution of fear memories when administered concurrently during extinction learning paradigms, suggesting that it may play a role in augmenting the effects of cognitive-behavioral therapy.[77] In a 2017 meta-analysis of the efficacy of D-cycloserine in augmentation of cognitive-behavioral therapy with or without an SSRI, it was found that doses of D-cycloserine between 50 mg/d and 250 mg/d were associated with a small antianxiety effect compared to placebo.[78] Interestingly, the effect of D-cycloserine was not moderated by the dose or the concurrent use of SSRIs, suggesting it may play a specific role in enhancing psychotherapy for those with anxiety disorders. Further research is needed to determine the proper sequence of treatments beyond first-line options.

KEY POINTS

- The risk of suicide is increased in those with anxiety disorders, especially in cases of a comorbid mood disorder or substance abuse.
- Benzodiazepines should be avoided in those with alcohol or substance abuse and should be used with caution in the elderly.
- A lack of response to an adequate course of either psychotherapy or medication should prompt a reexamination of the diagnosis, confirmation of treatment adherence, and ruling out of latent comorbid factors.
- Options for those with a lack of response to treatment for an anxiety disorder may include (1) switching from medication to psychotherapy or vice versa, (2) combining medication and psychotherapy, (3) switching between antidepressant medication classes, or (4) adding a medication to an antidepressant or psychotherapy to augment its effects.

CONCLUSION

Anxiety is often a transient response to perceived threats, which coordinates a set of psychological, behavioral, and biological reactions to prepare the individual

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to mount an adaptive response to a stressor. However, if this process becomes more context-independent, prolonged, excessive, and more difficult to regulate, it can become an anxiety disorder. *DSM-5* recognizes nine distinct anxiety disorder diagnoses, which share the common elements of acute distress, physical manifestations of fear, anticipatory worry, and avoidance of the anxiety-provoking stimuli. Anxiety disorders often manifest early in life and are chronic but treatable conditions, amenable to both psychological and biological approaches. Evidence-based treatments for anxiety disorders include cognitive-behavioral therapy and medications (SSRIs, SNRIs, benzodiazepines, and azapirones), which may exert their effects either through enhanced top-down cortical modulation of amygdala activity or via decreased bottom-up automatic negative reactivity to threat stimuli. Initial treatment selection may be guided by the severity of anxiety symptoms, the presence of comorbidities, and an individualized risk-benefit consideration of potential side effects of medications. A lack of consensus exists regarding next steps for treatment-resistant anxiety disorders, but therapeutic options include combining cognitive-behavioral therapy and antidepressant medication and add-on augmentation strategies, such as pregabalin, gabapentin, and quetiapine. More research in anxiety disorders is needed to address the unmet needs of biological tests to aid in diagnosis and treatment selection and the development of novel anxiolytic treatments and to further refine our knowledge on the optimal means of combining and sequencing existing treatments.

USEFUL WEBSITES

ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA
The Anxiety and Depression Association of America website provides resources for understanding depression, anxiety, and stress; information about suicide prevention; and links for treatment and support.
adaa.org

MOODGYM
MoodGym is a free online cognitive-behavioral therapy resource.
moodgym.com.au

NATIONAL INSTITUTE OF MENTAL HEALTH
The National Institute of Mental Health webpage on anxiety disorders provides educational resources, including signs and symptoms, risk factors, and treatments and therapies. It also includes information on how to join a clinical trial for anxiety disorders.
nimh.nih.gov/health/topics/anxiety-disorders/index.shtml

REFERENCES

1 Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety 2017;34(1):9–24. doi:10.1002/da.22556.

2 Baxter AJ, Vos T, Scott KM, et al. The global burden of anxiety disorders in 2010. Psychol Med 2014;44(11):2363–2374. doi:10.1017/S0033291713003243.

3 Browning M, Behrens TE, Jocham G, et al. Anxious individuals have difficulty learning the causal statistics of aversive environments. Nat Neurosci 2015;18(4):590–596. doi:10.1038/nn.3961.

4 Huang H, Thompson W, Paulus MP. Computational dysfunctions in anxiety: failure to differentiate signal from noise. Biol Psychiatry 2017;82(6):440–446. doi:10.1016/j.biopsych.2017.07.007.

5 Craske MG, Stein MB. Anxiety. Lancet 2016;388(10063):3048–3059. doi:10.1016/S0140-6736(16)30381-6.

6 Robinson OJ, Letkiewicz AM, Overstreet C, et al. The effect of induced anxiety on cognition: threat of shock enhances aversive processing in healthy individuals. Cogn Affect Behav Neurosci 2011;11(2):217–227. doi:10.3758/s13415-011-0030-5.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

7 Vytal KE, Overstreet C, Charney DR, et al. Sustained anxiety increases amygdala-dorsomedial prefrontal coupling: a mechanism for maintaining an anxious state in healthy adults. J Psychiatry Neurosci 2014;39(5):321–329. doi:10.1503/jpn.130145.

8 Robinson OJ, Krimsky M, Lieberman L, et al. Towards a mechanistic understanding of pathological anxiety: the dorsal medial prefrontal-amygdala 'aversive amplification' circuit in unmedicated generalized and social anxiety disorders. Lancet Psychiatry 2014;1(4): 294–302. doi:10.1016/S2215-0366(14)70305-0.

9 Fonzo GA, Ramsawh HJ, Flagan TM, et al. Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. Br J Psychiatry 2015; 206(3):206–215. doi:10.1192/bjp.bp.114.149880.

10 McCabe C, Mishor Z, Filippini N, et al. SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex. Mol Psychiatry 2011;16(6):592–594. doi:10.1038/mp.2010.138.

11 Doerig N, Krieger T, Altenstein D, et al. Amygdala response to self-critical stimuli and symptom improvement in psychotherapy for depression. Br J Psychiatry 2016;208(2):175–181. doi:10.1192/bjp.bp.114.149971.

12 Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 2016; 41(1):297–319. doi:10.1038/npp.2015.266.

13 Micco JA, Henin A, Mick E, et al. Anxiety and depressive disorders in offspring at high risk for anxiety: a meta-analysis. J Anxiety Disord 2009; 23(8):1158–1164. doi:10.1016/j.janxdis.2009.07.021.

14 Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. JAMA 2016;315(1):68–76. doi: 10.1001/jama.2015.17703.

15 Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157(10): 1552–1562. doi:10.1176/appi.ajp.157.10.1552.

16 Murphy SE, Norbury R, Godlewska BR, et al. The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: a meta-analysis. Mol Psychiatry 2013;18 (4):512–520. doi:10.1038/mp.2012.19.

17 Clauss JA, Avery SN, Blackford JU. The nature of individual differences in inhibited temperament and risk for psychiatric disease: a review and meta-analysis. Prog Neurobiol 2015;127–128: 23–45. doi:10.1016/j.pneurobio.2015.03.001.

18 Burkholder AR, Koss KJ, Hostinar CE, et al. Early life stress: effects on the regulation of anxiety expression in children and adolescents. Soc Dev 2016;25(4):777–793. doi:10.1111/sode.12170.

19 Tottenham N, Hare TA, Millner A, et al. Elevated amygdala response to faces following early deprivation. Dev Sci 2011;14(2):190–204. doi: 10.1111/j.1467-7687.2010.00971.x.

20 Gee DG, Gabard-Durnam LJ, Flannery J, et al. Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci U S A 2013;110(39): 15638–15643. doi:10.1073/pnas.1307893110.

21 Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. Psychiatr Clin North Am 2009;32(3): 483–524. doi:10.1016/j.psc.2009.06.002.

22 Chen LP, Murad MH, Paras ML, et al. Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clin Proc 2010;85(7):618–629. doi:10.4065/mcp.2009.0583.

23 McLaughlin KA, Conron KJ, Koenen KC, Gilman SE. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. Psychol Med 2010;40(10):1647–1658. doi:10.1017/S0033291709992121.

24 Richter P, Ramos RT. Obsessive-compulsive disorder. Continuum (Minneap Minn) 2018;24(3 Behavioral Neurology and Psychiatry):828–844.

25 Ellis J, Zaretsky A. Assessment and management of posttraumatic stress disorder. Continuum (Minneap Minn) 2018;24(3 Behavioral Neurology and Psychiatry):873–892.

26 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Washington, DC: American Psychiatric Association, 2013.

27 Giacobbe P, McIntyre RS, Goldstein BI, et al. Rates and patterns of treatment seeking by individuals with mood and anxiety disorders. Psychiatr Serv 2008;59(10):1099. doi:10.1176/appi.ps.59.10.1099.

28 White WB, Baker LH. Ambulatory blood pressure monitoring in patients with panic disorder. Arch Internal Med 1987;147(11):1973–1975. doi:10.1001/archinte.147.11.1973.

29 Nakamura M, Sugiura T, Nishida S, et al. Is nocturnal panic a distinct disease category? Comparison of clinical characteristics among patients with primary nocturnal panic, daytime panic, and coexistence of nocturnal and daytime panic. J Clin Sleep Med 2013;9(5): 461–467. doi:10.5664/jcsm.2666.

30 Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med 2013; 43(5):897–910. doi:10.1017/S003329171200147X.

31 Katon WJ. Clinical practice. Panic disorder. N Engl J Med 2006;354(22):2360–2367. doi:10.1056/NEJMcp052466.

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32 Imai H, Tajika A, Chen P, et al. Psychological therapies versus pharmacological interventions for panic disorder with or without agoraphobia in adults. Cochrane Database Syst Rev 2016;10: CD011170. doi:10.1002/14651858.CD011170.pub2.

33 Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014;(14 suppl 1):S1. doi:10.1186/1471-244X-14-S1-S1.

34 Nay W, Brown R, Roberson-Nay R. Longitudinal course of panic disorder with and without agoraphobia using the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Psychiatry Res 2013;208(1):54-61. doi:10.1016/j.psychres.2013.03.006.

35 McCabe L, Cairney J, Veldhuizen S, et al. Prevalence and correlates of agoraphobia in older adults. Am J Geriatr Psychiatry 2006;14(6): 515-522. doi:10.1097/01. JGP.0000203177.54242.14.

36 Giacobbe P, Flint AJ. Panic disorder in the elderly. Aging Health 2007;3(2):245-255. doi: 10.2217/1745509X.3.2.245.

37 Goodwin H, Yiend J, Hirsch CR. Generalized anxiety disorder, worry and attention to threat: a systematic review. Clin Psychol Rev 2017;54: 107-122. doi:10.1016/j.cpr.2017.03.006.

38 Stein MB, Sareen J. Clinical practice. Generalized anxiety disorder. N Engl J Med 2015;373(21): 2059-2068. doi:10.1056/NEJMcp1502514.

39 Leichsenring F, Leweke F. Social anxiety disorder. N Engl J Med 2017;376(23):2255-2264. doi:10.1056/NEJMcp1614701.

40 Steinert C, Hofmann M, Leichsenring F, Kruse J. What do we know today about the prospective long-term course of social anxiety disorder? A systematic literature review. J Anxiety Disord 2013;27(7):692-702. doi:10.1016/j. janxdis.2013.08.002.

41 Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166 (10):1092-1097. doi:10.1001/archinte.166.10.1092.

42 Stein MB, Craske MG. Treating anxiety in 2017: optimizing care to improve outcomes. JAMA 2017;318(3):235-236. doi:10.1001/ jama.2017.6996.

43 Wardenaar KJ, Lim CCW, Al-Hamzawi AO, et al. The cross-national epidemiology of specific phobia in the World Mental Health Surveys. Psychol Med 2017;47(10):1744-1760. doi:10.1017/ S0033291717000174.

44 Donadio V, Liguori R, Elam M, et al. Arousal elicits exaggerated inhibition of sympathetic nerve activity in phobic syncope patients. Brain 2007;130(pt 6):1653-1662. doi:10.1093/brain/ awm037.

45 Beesdo K, Pine DS, Lieb R, Wittchen HU. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. Arch Gen Psychiatry 2010;67(1):47-57. doi:10.1001/ archgenpsychiatry.2009.177.

46 Hannigan LJ, Walaker N, Waszczuk MA, et al. Aetiological influences on stability and change in emotional and behavioural problems across development: a systematic review. Psychopathol Rev 2017;4(1):52-108. doi:10.5127/ pr.038315.

47 Hua A, Major N. Selective mutism. Curr Opin Pediatr 2016;28(1):114-120. doi:10.1097/ MOP.0000000000000300.

48 Steinhausen HC, Wachter M, Laimböck K, Metzke CW. A long-term outcome study of selective mutism in childhood. J Child Psychol Psychiatry 2006;47(7):751-756. doi:10.1111/ j.1469-7610.2005.01560.x.

49 Manassis K, Oerbeck B, Overgaard KR. The use of medication in selective mutism: a systematic review. Eur Child Adolesc Psychiatry 2016;25(6): 571-578. doi:10.1007/s00787-015-0794-1.

50 Baldwin DS, Gordon R, Abelli M, Pini S. The separation of adult separation anxiety disorder. CNS Spectr 2016;21(4):289-294. doi:10.1017/ S1092852916000080.

51 Silove D, Alonso J, Bromet E, et al. Pediatric-onset and adult-onset separation anxiety disorder across countries in the World Mental Health Survey. Am J Psychiatry 2015;172(7): 647-656. doi:10.1176/appi.ajp.2015.14091185.

52 Milrod B, Markowitz JC, Gerber AJ, et al. Childhood separation anxiety and the pathogenesis and treatment of adult anxiety. Am J Psychiatry 2014;171(1):34-43. doi:10.1176/ appi.ajp.2013.13060781.

53 Battaglia M. Separation anxiety: at the neurobiological crossroads of adaptation and illness. Dialogues Clin Neurosci 2015;17(3):277-285.

54 Sobanski T, Wagner G. Functional neuroanatomy in panic disorder: status quo of the research. World J Psychiatry 2017;7(1):12-33. doi:10.5498/ wjp.v7.i1.12.

55 Bandelow B, Reitt M, Röver C, et al. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol 2015;30(4): 183-192. doi:10.1097/YIC.0000000000000078.

56 Cuijpers P, Gentili C, Banos RM, et al. Relative effects of cognitive and behavioral therapies on generalized anxiety disorder, social anxiety disorder and panic disorder: a meta-analysis. J Anxiety Disord 2016;43:79-89. doi:10.1016/j. janxdis.2016.09.003.

57 Barlow DH, Farchione TJ, Bullis JR, et al. The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders: a randomized clinical trial. JAMA Psychiatry 2017;74(9):875-884. doi:10.1001/ jamapsychiatry.2017.2164.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

58 McHugh RK, Whitton SW, Peckham AD, et al. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. J Clin Psychiatry 2013;74(6):595–602. doi:10.4088/JCP.12r07757.

59 Wootton BM, Titov N, Dear BF, et al. An Internet administered treatment program for obsessive-compulsive disorder: a feasibility study. J Anxiety Disord 2011;25(8):1102–1107. doi:10.1016/j.janxdis.2011.07.009.

60 Peñate W, Fumero A. A meta-review of Internet computer-based psychological treatments for anxiety disorders. J Telemed Telecare 2016;22(1):3–11. doi:10.1177/1357633X15586491.

61 Zeidan F, Martucci KT, Kraft RA, et al. Neural correlates of mindfulness meditation-related anxiety relief. Soc Cogn Affect Neurosci 2014;9(6):751–759. doi:10.1093/scan/nst041.

62 Steinert C, Munder T, Rabung S, et al. Psychodynamic therapy: as efficacious as other empirically supported treatments? A meta-analysis testing equivalence of outcomes. Am J Psychiatry 2017;174(10):943–953. doi:10.1176/appi.ajp.2017.17010057.

63 Health Canada Advisory; Recalls and safety alerts. Public communication—Health Canada endorsed important safety information on Celexa (citalopram). *healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/16887a-eng.php*. Published January 30, 2012. Updated March 4, 2013. Accessed April 2, 2018.

64 Health Canada Advisory; Recalls and safety alerts. Antidepressant Cipralex (escitalopram): updated information regarding dose-related heart risk. *healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/13674a-eng.php*. Published May 7, 2012. Updated March 30, 2013. Accessed April 2, 2018.

65 US Food and Drug Administration. FDA Drug Safety Communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. *www.fda.gov/Drugs/DrugSafety/ucm297391.htm*. Published March 28, 2012. Updated January 7, 2016. Accessed April 2, 2018.

66 US Food and Drug Administration. Escitalopram oxalate prescribing information. *www.accessdata.fda.gov/drugsatfda_docs/label/2017/021323s047lbl.pdf*. Revised January 2017. Accessed April 2, 2018.

67 Kanwar A, Malik S, Prokop LJ, et al. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety 2013;30(10):917–929. doi:10.1002/da.22074.

68 Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry 2008;192(2):98–105. doi:10.1192/bjp.bp.107.040113.

69 Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry 2015;72(2):136–142. doi:10.1001/jamapsychiatry.2014.1763.

70 Bushnell GA, Stürmer T, Gaynes BN, et al. Simultaneous antidepressant and benzodiazepine new use and subsequent long-term benzodiazepine use in adults with depression, United States, 2001–2014. JAMA Psychiatry 2017;74(7):747–755. doi:10.1001/jamapsychiatry.2017.1273.

71 Chen MH, Tsai SJ. Treatment-resistant panic disorder: clinical significance, concept and management. Prog Neuropsychopharmacol Biol Psychiatry 2016;70:219–226. doi:10.1016/j.pnpbp.2016.02.001.

72 Santana L, Fontenelle LF. A review of studies concerning treatment adherence of patients with anxiety disorders. Patient Prefer Adherence 2011;5:427–439. doi:10.2147/PPA.S23439.

73 Issakidis C, Andrews G. Pretreatment attrition and dropout in an outpatient clinic for anxiety disorders. Acta Psychiatr Scand 2004;109(6):426–433. doi:10.1111/j.1600-0047.2004.00264.x.

74 Stein MB, Cantrell CR, Sokol MC, et al. Antidepressant adherence and medical resource use among managed care patients with anxiety disorders. Psychiatr Serv 2006;57(5):673–680. doi:10.1176/ps.2006.57.5.673.

75 Mitchell AJ, Selmes T. A comparative survey of missed initial and follow-up appointments to psychiatric specialties in the United Kingdom. Psychiatr Serv 2007;58(6):868–871. doi:10.1176/ps.2007.58.6.868.

76 Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry 2010;71(7):839–854. doi:10.4088/JCP.10r06218blu.

77 Otto MW, Kredlow MA, Smits JA, et al. Enhancement of psychosocial treatment with D-cycloserine: models, moderators, and future directions. Biol Psychiatry 2016;80(4):274–283. doi:10.1016/j.biopsych.2015.09.007.

78 Mataix-Cols D, Fernández de la Cruz L, Monzani B, et al. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: a systematic review and meta-analysis of individual participant data. JAMA Psychiatry 2017;74(5):501–510. doi:10.1001/jamapsychiatry.2016.3955.

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