Chapter 90: Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 67, Anxiety Disorders.

KEY CONCEPTS

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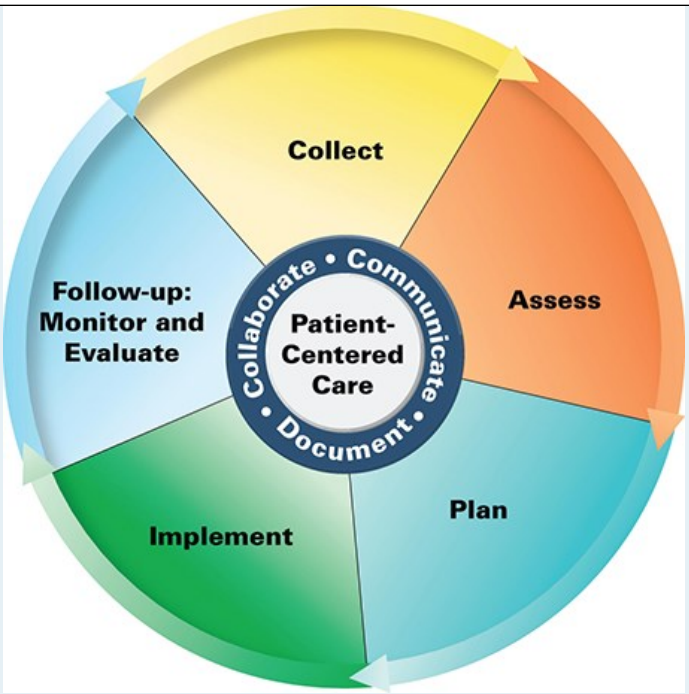
1. Anxiety disorders are among the most common psychiatric disorders and are underdiagnosed and undertreated.
2. The long-term goal in treatment of generalized anxiety disorder (GAD) is remission with minimal or no anxiety symptoms and no functional impairment.
3. Antidepressants are the agents of choice for the management of GAD.
4. In GAD, antidepressants have a lag time of 2 to 4 weeks or longer before antianxiety effects occur.
5. When monitoring the effectiveness of antidepressants in panic disorder, it is important to allow an adequate amount of time (8-12 weeks) to achieve full therapeutic response.
6. The optimal duration of panic therapy is unknown; 12 to 24 months of pharmacotherapy is recommended before gradual medication discontinuation over 4 to 6 months is attempted.
7. Social anxiety disorder (SAD) is a chronic long-term illness requiring extended therapy. After improvement, a 6- to 12-month or longer medication maintenance period is recommended before considering treatment discontinuation.
8. The selective serotonin reuptake inhibitors or venlafaxine are considered first-line pharmacotherapy for SAD.
9. An adequate trial of antidepressants in SAD lasts at least 8 weeks, and maximal benefit may not be seen until 12 weeks.
10. In SAD, the three principal domains in which improvement should be observed are symptoms, functionality, and well-being.

PATIENT CARE PROCESS

Patient Care Process for Anxiety Disorders



Collect

- Patient characteristics (eg, age, sex, pregnancy)
- Patient medical history (personal and family)
- Patient psychiatric history (personal and family)
- Social history (eg, caffeine, nicotine, ethanol, or other substance use including route of administration)
- Current medications including over-the-counter (OTC), herbal products, dietary supplements, and prior psychiatric medication use
- Mental status examination
- Objective data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, and weight
    - Labs including thyroid stimulating hormone (TSH)
    - Urinalysis including urine medications testing
    - Generalized Anxiety Disorder 7-Item Scale, Hamilton Anxiety Disorder Rating Scale (HAM-A), Sheehan Disability Scale, and Patient Health Questionnaire-9 (PHQ-9)

Assess

- Presence of generalized anxiety disorder, panic disorder, or social anxiety disorder
- Presence of comorbid depression or substance use disorder
- Ability/willingness to begin nonpharmacologic treatments, including availability in geographic region
- Ability/willingness to begin pharmacologic treatment

- Ability/willingness to afford nonpharmacologic and/or pharmacologic treatment(s)
- Support of family members/caregivers for treatment

Plan*

- Pharmacotherapy regimen including specific medication(s), dose, route, frequency, and duration (see Fig. 90-1, and Tables 90-4, 90-5, 90-8, and 90-9)
- Monitoring parameters including efficacy (eg, rating scales, quality of life)
- Patient education (eg, disease, life style changes, medication adherence, when to expect medication to begin working, possible adverse reactions, expected duration of therapy, when to contact healthcare professional)
- Self-monitoring for resolution of anxiety symptoms

Implement*

- Provide patient education regarding all aspects of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of anxiety symptoms
- Presence of adverse medication reactions (eg, sedation, psychomotor impairment, nausea, headaches, weight gain, sexual dysfunction)
- Psychiatric rating scale results
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate in 2 weeks until stable, then every 3 months

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Visit the National Institute of Mental Health (NIMH) website for Anxiety Disorders (https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml) and review the patient brochures for generalized anxiety disorder and panic disorder. Compare and contrast the signs and symptoms and the available treatment options for these two anxiety disorders. This activity will help you to differentiate the clinical presentation of each disorder and assist you with the ASSESS portion of the "Patient Care Process."

Complete the case "Bundle of Nerves" in Pharmacotherapy Casebook: A Patient-Focused Approach. This activity will help you to practice the ASSESS, PLAN, and MONITOR portions of the "Patient Care Process."

INTRODUCTION

Anxiety is an emotional state commonly caused by the perception of real or perceived danger that threatens the security of an individual. It allows a

person to prepare for or react to environmental changes. Everyone experiences a certain amount of nervousness and apprehension when faced with a stressful situation. This is an adaptive response and is transient in nature.

Anxiety can produce uncomfortable and potentially debilitating psychological (eg, worry or feeling of threat) and physiologic arousal (eg, tachycardia or shortness of breath) if it becomes excessive. Some individuals experience persistent, severe anxiety symptoms and possess irrational fears that significantly impair normal daily functioning. These persons often suffer from an anxiety disorder.[1]

1 Anxiety disorders are among the most frequent psychiatric disorders encountered in clinical practice and are often underdiagnosed and undertreated.[2] Healthcare professionals often mistake anxiety disorders for physical illnesses, and less than one-third of patients receive appropriate treatment.[2] Failure to diagnose and manage anxiety disorders results in negative outcomes including overuse of healthcare resources, increased risk for suicide, and substance use disorders (SUDs).[3] Individuals with anxiety disorders develop cardiovascular, cerebrovascular, gastrointestinal (GI), and respiratory disorders at a significantly higher rate than the general population.[3]

To treat anxiety appropriately, the clinician must make a reliable diagnosis. Understanding the distinction between short-term symptoms of anxiety and anxiety disorders is essential. Common or situational anxiety is a normal response to a stressful circumstance. Although symptoms can be severe, they are temporary and usually last no more than 2 or 3 weeks. In this situation, short-term, "as-needed" treatment with an anxiolytic agent such as a benzodiazepine is common and can provide some symptomatic relief; prolonged medication therapy is not recommended for situational anxiety.[4]

EPIDEMIOLOGY

Anxiety disorders, as a group, are the most commonly occurring psychiatric disorders as approximately 34% of the population are affected by an anxiety disorder during their lifetime.[5] According to the National Comorbidity Survey Replication which assessed the prevalence, severity, and comorbidity estimates of mental disorders in the United States, the most recent 1-year prevalence rate for anxiety disorders was 21.3% in persons aged 18 years and older. Specific phobias were the most common anxiety disorder, with a 12-month prevalence of 10.1%. The 1-year prevalence of generalized anxiety disorder (GAD) was 2.9%, panic disorder was 3.1%, and social anxiety disorder (SAD) was 8.0%.[5]

In general, anxiety disorders are a group of heterogeneous illnesses that develop before age 30 years and are more common in females, individuals with social issues, and those with a family history of anxiety and depression. Patients often develop another anxiety disorder, major depression, or SUDs.[1,2] The clinical picture of mixed anxiety and depression is much more common than an isolated anxiety disorder.[6,7]

ETIOLOGY

The differential diagnosis of anxiety disorders includes medical and psychiatric illnesses and certain medications or substances.[6,7] Hypotheses on the etiology of anxiety disorders are based on interactions between a combination of factors including vulnerability (eg, genetic predisposition and early childhood adversity) and stress (eg, occupational and traumatic experience). The vulnerability may be associated with genetic factors and neurobiologic adaptations of the central nervous system (CNS).[8]

Medical Diseases Associated with Anxiety

Anxiety symptoms are an inherent part of the initial clinical presentation of several diseases, which complicates the distinction between anxiety disorders and medical disorders.[4,7] Furthermore, anxiety disorders are associated with chronic medical illness, low levels of physical health-related quality of life (QOL), and physical disability.[2] If anxiety symptoms are secondary to a medical illness, they usually will subside as the medical situation stabilizes. However, the knowledge that one has a physical illness can trigger anxious feelings and further complicate therapy. Persistent anxiety subsequent to a physical illness requires further assessment for an anxiety disorder. Common somatic symptoms of anxiety that frequently present in medical disorders include abdominal pain, palpitations, tachycardia, sweating, flushing, tremor, chest pain or tightness, and shortness of breath. Although less specific, symptoms of muscle tension, headache, and fatigue are also common manifestations of anxiety. Medical disorders most closely associated with anxiety are listed in Table 90-1.

TABLE 90-1

Common Medical Illnesses Associated with Anxiety Symptoms

Cardiovascular • Angina, arrhythmias, cardiomyopathy, congestive heart failure, hypertension, ischemic heart disease, mitral valve prolapse, myocardial infarction
Endocrine and metabolic • Cushing disease, diabetes, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B_{12} or folate deficiencies
Gastrointestinal • Crohn's disease, irritable bowel syndrome, ulcerative colitis, peptic ulcer disease
Neurologic • Migraine, seizures, stroke, neoplasms, poor pain control
Respiratory system • Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia
Others • Anemias, cancer, systemic lupus erythematosus, vestibular dysfunction

Data from References 3,6, and 7.

Psychiatric Diseases Associated with Anxiety

Anxiety can be a presenting feature of several major psychiatric illnesses. Anxiety symptoms are extremely common in patients with mood disorders, schizophrenia, dementia, and SUDs. Most patients with psychiatric illness will have two or more concurrent (comorbid) psychiatric disorders within their lifetime.[5] It is important to diagnose and treat all comorbid psychiatric conditions in patients with anxiety disorders.

Medication- and Substance-Induced Anxiety

Medications and substances are a common cause of anxiety symptoms (Table 90-2). While anxiety occurs during the use of CNS-stimulants in a dose-dependent manner, ingestion of minimal amounts can result in marked anxiety, including panic attacks, in some individuals. The onset of medication-induced anxiety is usually rapid after the initiation of therapy. A thorough medication history evaluating for a recently initiated medication or dosage change as well as unhealthy substance use is important to rule out a medication- or unhealthy substance-induced etiology for the anxiety.

TABLE 90-2

Medications and Substances Associated with Anxiety Symptoms

Antiseizure medications: Carbamazepine, phenytoin
Antidepressants: Bupropion, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors
Antihypertensives: Clonidine, felodipine
Antibiotics: Quinolones, isoniazid
Bronchodilators: Albuterol, theophylline
Corticosteroids: Prednisone
Dopamine agonists: Amantadine, levodopa
Herbals: Ginseng, ephedra
Unhealthy substance use: Ecstasy, cannabis, cocaine
Nonsteroidal anti-inflammatory medications: Ibuprofen, indomethacin
Stimulants: Amphetamines, caffeine, methylphenidate, nicotine
Sympathomimetics: Pseudoephedrine, phenylephrine
Thyroid hormones: Levothyroxine
Toxicity: Anticholinergics, antihistamines, digoxin

Data from References 1 and 4.

Anxiety occurs occasionally during the use of CNS depressants, especially in children and older adults; however, anxiety symptoms are more common as complications of withdrawal after the abrupt discontinuation of these agents.[6]

PATHOPHYSIOLOGY

The modulation of normal and pathologic anxiety states is associated with multiple regions of the brain and abnormal function in several neurotransmitter systems, including norepinephrine (NE), γ-aminobutyric acid (GABA), serotonin (5-HT), dopamine (DA), corticotropin-releasing factor (CRF), and cholecystokinin.[9] Neuroanatomic models of fear (ie, the response to danger) and anxiety (ie, the feeling of fear that is disproportionate to the actual threat) include some key brain areas. The amygdala, a temporal lobe structure, plays a critical role in the assessment of fear stimuli and learned response to fear.[9,10] The locus ceruleus (LC), located in the brain stem, is the primary NE-containing site, with widespread projections to areas responsible for implementing fear responses (eg, vagus, lateral, and paraventricular hypothalamus). The hippocampus is integral in the consolidation of traumatic memory and contextual fear conditioning. The hypothalamus is the principal area for integrating neuroendocrine and autonomic responses to a threat.[9] Recent reviews of potential biomarkers for anxiety disorders in neurochemistry, genetics, and neuroimaging report insufficient evidence of specific biomarkers for diagnosis and treatment response.[11,12]

Neurochemical Theories

Noradrenergic Model

The basic premise of the noradrenergic theory is that the autonomic nervous system of patients with anxiety disorders is hypersensitive and overreacts to various stimuli. Many patients with anxiety disorders clearly display symptoms of peripheral autonomic hyperactivity. In response to threat or fearful situations, the LC serves as an alarm center, activating NE release and stimulating the sympathetic and parasympathetic nervous systems. Chronic central noradrenergic overactivity downregulates α_2-adrenoreceptors in patients with GAD. This receptor is hypersensitive in some patients with panic disorder.[9] By administering medications that have a relatively specific effect on the LC, researchers have further explored the NE theory of anxiety and panic disorder. Medications with anxiogenic effects (eg, yohimbine [an α_2-adrenergic receptor antagonist]) stimulate LC firing and increase noradrenergic activity. The resultant NE release in turn increases glutamate release (an excitatory neurotransmitter).[9] This produces subjective feelings of anxiety and can precipitate a panic attack in those with panic disorder, but not in normal volunteers.[9] Medications with anxiolytic or

antipanic effects (eg, benzodiazepines and antidepressants) inhibit LC firing, decrease noradrenergic activity, and block the effects of anxiogenic agents.[9]

GABA-Receptor Model

The major inhibitory neurotransmitter in the CNS, GABA has a strong regulatory or inhibitory effect on the 5-HT, NE, and DA systems. There are two superfamilies of GABA-protein receptors: $GABA_A$ and $GABA_B$. Medications that reduce anxiety and produce sedation target the $GABA_A$ receptor. The $GABA_A$ receptors are ligand-gated ion channels composed of five protein subunits. Several classes of subunits (ie, α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π, ρ_{1-3}) surround a central pore, and the receptor is connected to the cytoskeleton.[13] When GABA binds to the $GABA_A$ receptor, neuronal excitability is reduced. Benzodiazepine ligands enhance the inhibitory effects of GABA.[13] The $GABA_B$ receptor is a G-protein–coupled receptor postulated to be involved in the presynaptic inhibition of GABA release[9,13]

The specific role of the GABA receptors in anxiety disorders has not been established. The number of $GABA_A$ receptors can change with alterations in the environment (eg, chronic stress), and the subunit expression can be altered by hormonal changes.[13] Reductions in benzodiazepine binding and GABA concentrations in the brain are reported in patients with panic disorder.[11]

Serotonin Model

Although there are data suggesting that the 5-HT system is dysregulated in patients with anxiety disorders, definitive evidence that shows a clear abnormality in 5-HT function is lacking. In general, 5-HT is primarily an inhibitory neurotransmitter that is used by neurons originating in the raphe nuclei of the brain stem and projecting diffusely throughout the brain (eg, cortex, amygdala, hippocampus, and limbic system). Abnormalities in serotonergic functioning through release and uptake at the presynaptic autoreceptors ($5\text{-}HT_{1A/1D}$), the serotonin-reuptake transporter (SERT), or effect of 5-HT at the postsynaptic receptors (eg, $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, and $5\text{-}HT_{2C}$) may play a role in anxiety disorders.[9,11] Greater 5-HT function may facilitate avoidance behavior; however, reducing 5-HT may increase aggression.[9] Greater 5-HT activity reduces NE activity in the LC, inhibits defense/escape response via the periaqueductal gray (PAG) region, and reduces hypothalamic release of CRF. The selective serotonin reuptake inhibitors (SSRIs) acutely increase 5-HT levels by blocking the SERT to increase the amount of 5-HT available postsynaptically and are efficacious in blocking the manifestations of panic and anxiety.[9]

Low 5-HT activity may lead to a dysregulation of other neurotransmitters. Both the NE and 5-HT systems are closely linked, and interactions between the two are reciprocal and vary. As NE may act at presynaptic 5-HT terminals to decrease 5-HT release, its activity at postsynaptic receptors can cause increased 5-HT release.

Buspirone is a selective $5\text{-}HT_{1A}$ partial agonist that is effective for GAD but not for panic disorder.[14] Because the selective $5\text{-}HT_{1A}$ partial agonists reduce serotonergic activity, GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways. There is circumstantial evidence for the involvement of serotonergic and dopaminergic systems in the pathophysiology of generalized SAD.[15]

Neuroimaging Studies

Functional neuroimaging studies support the crucial role of the amygdala, anterior cingulate cortex (ACC), ventromedial prefrontal cortex, and insula in the pathophysiology of anxiety.[8,11] In GAD there is an abnormal increase in the brain's fear circuitry, as well as decreased activity in the prefrontal cortex, which appears to have a compensatory role in reducing GAD symptoms.[16] Patients with panic have abnormalities of midbrain structures, including the PAG. Neuroimaging studies have shown activation of insula and upper brain stem (including the PAG), as well as deactivation of the ACC during experimental panic attacks.[10] Patients with SAD have greater activity than matched comparison subjects in the amygdala and insula, structures linked to negative emotional responses.[11] Both pharmacotherapy and psychotherapy decrease cerebral blood flow in the amygdala, hippocampus, and surrounding cortical areas in patients with SAD.[8,11]

CLINICAL PRESENTATION

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* classifies anxiety disorders into categories including GAD, panic disorder, agoraphobia, SAD, specific phobia, and separation anxiety disorder.[1] The characteristic features of these illnesses are anxiety and avoidance behavior. Anxiety symptoms must cause significant distress and impairment in social, occupational, or other areas of functioning, and should not be secondary to a medication or unhealthy substance use or a general medical disorder or occur solely as part of another psychiatric disorder.[1] The anxiety-related syndromes, posttraumatic stress disorder, and obsessive-compulsive disorder are discussed in Chapter 91 "Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder."

Generalized Anxiety Disorder

The diagnostic criteria for GAD require persistent symptoms for most days for at least 6 months.[1] The essential feature of GAD is unrealistic or excessive anxiety and worry about a number of events or activities.[1] The anxiety or apprehensive expectation is accompanied by at least three psychological or physical symptoms. Anxiety and worry are not confined to features of another psychiatric illness (eg, having a panic attack, being embarrassed in public).[1]

The onset, course of illness, and comorbid conditions of GAD are important considerations. While GAD has a gradual onset with an average age of 21 years, there is a bimodal distribution. Onset occurs earlier when GAD is the primary presentation and later when GAD is secondary. In general, GAD can be exacerbated or precipitated in later life by severe psychological stressors. Most patients present between the ages of 35 and 45 years, with females twice as likely to have GAD as males. The course of the illness is chronic (ie, episodes can last for a decade or longer) and there is a high percentage of relapse with low overall rates of recovery.[1] Patients report substantial interference with their lives and have a high probability of seeking treatment. Lifetime comorbidity with another psychiatric disorder occurs in 90% of patients with GAD, with depression in over 50%.[17]

CLINICAL PRESENTATION: Generalized Anxiety Disorder

Psychological and Cognitive Symptoms

- Excessive anxiety
- Worries that are difficult to control
- Feeling keyed up or on edge
- Trouble concentrating or mind going blank

Physical Symptoms

- Restlessness
- Fatigue
- Muscle tension
- Sleep disturbance
- Irritability

Data from References 1, 2, and 3.

Panic Disorder

Panic disorder begins as a series of unexpected (spontaneous) panic attacks involving an abrupt surge of intense fear or intense discomfort. The unexpected panic attacks are followed by at least 1 month of persistent concern about having another panic attack, worry about the possible consequences of the panic attack, or a significant maladaptive change in behavior related to the attacks.[1] During an attack, patients describe at least four psychological and physical symptoms. Panic attacks usually last no more than 20 to 30 minutes, with the peak intensity of symptoms within the first 10 minutes. Often patients seek help at a physician's office or emergency department, only to have their symptoms resolve before or on arrival. Because panic symptoms mimic those of several medical conditions, patients often are misdiagnosed, and multiple referrals are common.[1]

Up to 50% of patients develop agoraphobia secondary to the panic attacks.[1] Agoraphobia is marked fear or anxiety about being in at least two situations in which escape might be difficult or where help might not be available in the event of developing panic-like symptoms.[1] As a result, patients often avoid specific situations (eg, using public transportation, being in open or enclosed places, being in a crowd or being outside of the home alone) in which they fear a panic attack might occur.[1]

Complications of panic disorder include depression (10%-65% have major depressive disorder), alcohol use disorder, and high use of health services and emergency rooms.[1] Patients with panic disorder have a high lifetime risk for suicide attempts compared with the general population.[1] The usual course is chronic but waxing and waning.

CLINICAL PRESENTATION: Panic Attack

Psychological Symptoms

- Depersonalization (being detached from oneself)
- Derealization (feelings of being detached from one's environment)
- Fear of losing control, going crazy, or dying

Physical Symptoms

- Abdominal distress
- Chest pain or discomfort
- Chills
- Dizziness or light-headedness
- Feeling of choking
- Heat sensations
- Nausea
- Palpitations
- Paresthesias
- Sensations of shortness of breath or smothering
- Sweating
- Tachycardia
- Trembling or shaking

Data from References 1, 2, and 3.

Social Anxiety Disorder

Social anxiety disorder is characterized by marked fear about one or more social situations in which the individual is exposed to possible scrutiny by others. Exposure to the feared circumstance usually provokes an immediate situation-related panic attack. Blushing is the principal physical indicator and distinguishes SAD from other anxiety disorders. The fear and anxiety are out of proportion to the actual threat posed by the social situation and is persistent, typically lasting for 6 months or longer.[1] If the fear is restricted to speaking or performing in public, the SAD is specified as performance only.

The mean age of onset of SAD is during the mid-teens with rates slightly higher among females than males and more frequent in younger cohorts. It is a chronic disorder with a mean duration of 20 years.[1] People with SAD can be reluctant to seek professional help despite the existence of beneficial treatments because consultation with a clinician is perceived as a feared social interaction.[18]

Differentiating SAD from other anxiety disorders can be difficult. Panic attacks occur in both SAD and panic disorder, but the distinction between the two is the rationale behind the fear, whereas fear of anxiety symptoms is characteristic of panic disorder and fear of embarrassment from social

interaction typifies SAD.[1] A majority of patients with SAD eventually develop a concurrent mood, anxiety, or SUD.[18]

CLINICAL PRESENTATION: Social Anxiety Disorder

Fears of Being

- Scrutinized by others
- Negatively evaluated (ie, humiliated, embarrassed, or rejected)

Some Feared Situations

- Eating or writing in front of others
- Interacting with authority figures
- Speaking in public
- Talking with strangers
- Use of public toilets

Symptoms of Anxiety

- Blushing
- "Butterflies in the stomach"
- Diarrhea
- Stumbling over words
- Sweating
- Tachycardia
- Trembling

Specifier

Performance; applies only if the fear is restricted to speaking or performing in public.

Data from References 1 and 18.

Specific Phobia

Specific phobia is marked and persistent fear of a circumscribed object or situation (eg, insects or heights). Apart from contact with the feared object or situation, the patient is usually free of symptoms. Most persons simply avoid the feared object and adjust to certain restrictions on their activities.[1]

TREATMENT—GENERALIZED ANXIETY DISORDER

Desired Outcomes

2 The goals of therapy in the acute management of GAD are to reduce the severity and duration of the anxiety symptoms and to improve overall

functioning. The long-term goal in GAD is remission with minimal or no anxiety symptoms, no functional impairment, and increased QOL.[17] Prevention of recurrence is another long-term consideration.

General Approach

Once GAD is diagnosed, a patient-specific treatment plan, which usually consists of both psychotherapy and pharmacotherapy, is developed. The plan depends on the severity and chronicity of symptoms, age, medication history, and comorbid medical and psychiatric conditions.[19] Factors such as anticipated adverse medication reactions, history of prior response in the patient or family member, patient preference, and cost should be considered when treatment is initiated. Psychotherapy is the least invasive and safest treatment modality. Antianxiety medication is indicated for patients experiencing symptoms severe enough to produce functional disability. Table 90-3 lists medication choices for GAD, panic disorder, and SAD.

TABLE 90-3

Medication Choices for Anxiety Disorders

Anxiety Disorder	First-Line Medications	Second-Line Medications	Alternatives
Generalized anxiety disorder	Duloxetine Escitalopram Paroxetine Sertraline Venlafaxine XR	Benzodiazepines Buspirone Imipramine Pregabalin	Hydroxyzine Quetiapine
Panic disorder	SSRIs Venlafaxine XR	Alprazolam Citalopram Clomipramine Clonazepam Imipramine	Phenelzine
Social anxiety disorder	Escitalopram Fluvoxamine CR Paroxetine Sertraline Venlafaxine XR	Clonazepam Citalopram	Gabapentin Phenelzine Pregabalin

CR, controlled-release; SSRI, selective serotonin reuptake inhibitor; XR, extended-release.

Data from References 2, 20, and 21.

The need for treatment is determined by patient-specific factors including severity and duration of symptoms, degree of disability, and the presence of coexisting disorders (ie, mood or other anxiety disorders). The patient should be assessed for response to or intolerance of previous treatment approaches. The selection of a specific treatment modality should be based on concurrent medical conditions, contraindications, patient's preference of treatment, and the availability of potential treatment options. The clinician should consider Food and Drug Administration (FDA) warnings (eg, QTc prolongation for citalopram and hydroxyzine, teratogenicity with paroxetine) and potential for adverse events with medical disease (eg, anticholinergic effects and weight gain with paroxetine in patients with diabetes, obesity, or benign prostatic hyperplasia) when selecting an agent. Increased risk of suicidality should be considered in patients taking antidepressants who are younger than 25 years of age. All patients should receive education that includes information about GAD, treatment choices, and resources for support in the community. The patient should be an integral part of decision making and should be informed about effectiveness, common adverse medication reactions, duration of treatment, costs associated with treatment, and what to expect when treatment is discontinued.[2]

Nonpharmacologic Therapy

Nonpharmacologic treatment modalities in GAD include psychoeducation, short-term counseling, stress management, psychotherapy, mindfulness-based therapy, or exercise. Psychoeducation includes information on the etiology and management of GAD (eg, Anxiety and Depression Association of America, www.adaa.org). For all anxiety and psychiatric disorders, peer-to-peer support obtained through the National Alliance for Mental Illness (NAMI) can be helpful (https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Peer-to-Peer). Patients with anxiety should be instructed to avoid caffeine, nicotine, nonprescription stimulants, diet pills, and excessive use of alcohol. Most patients with GAD require psychological therapy, alone or in combination with antianxiety medications, to overcome fears and to learn to manage their anxiety and worry.[22] Cognitive behavioral therapy (CBT) is the most effective psychological therapy in individuals with GAD. In general, CBT for GAD includes self-monitoring of worry, cognitive restructuring, relaxation training, and rehearsal of coping skills.[22] Psychotherapy or medication alone has comparable efficacy in acute treatment.[21] The relapse rate with CBT is less than with other types of psychological modalities.[21] Controlled trials comparing the efficacy of combining medication and psychotherapy over long-term treatment are lacking.[21] Advantages of CBT over pharmacotherapy include patient preference and lack of troubling adverse medication reactions. However, CBT is not widely available, requires specialized training, and entails weekly sessions for an extended time period (ie, 12-16 weeks).[23] Other options include group therapy (8-12 sessions) and computer-based therapy.[23]

Pharmacologic Therapy

The benzodiazepines are the most effective and commonly prescribed medications for the rapid relief of acute anxiety symptoms (Table 90-4). All benzodiazepines are equally effective anxiolytics, and consideration of pharmacokinetic properties and the patient's clinical situation will assist in the selection of the most appropriate agent.[17]

TABLE 90-4

Benzodiazepine Antianxiety Agents

Medication	Brand Name	Approved Dosage Range (mg/day)	Maximum Dosage for Geriatric Patients (mg/day)	Approximate Equivalent Dose (mg)	Comments
Alprazolam[a]	Xanax	0.75-4	2	0.5	Associated with interdose rebound anxiety
	Xanax XR	1-10[b]			
Chlordiazepoxide[a]	Librium	25-400	40	10	
Clonazepam[a]	Klonopin	1-4[b]	3	0.25-0.5	
	Klonopin Wafer[c]				
Clorazepate[a]	Tranxene	7.5-60	30	7.5	
Diazepam[a]	Valium	2-40	20	5	
Lorazepam[a]	Ativan	0.5-10	3	1	Preferred in older adults
Oxazepam[a]	Serax	30-120	60	30	Preferred in older adults

XR, extended-release.

[a]Available generically.

[b]Panic disorder dose.

[c]Orally disintegrating formulation.

Data from References 24-26.

As antidepressants lack the physical dependence and adverse medication reactions seen with benzodiazepines, they have emerged as the treatment of choice for the management of chronic anxiety, especially in the presence of comorbid depressive symptoms. Buspirone is an additional anxiolytic option (Table 90-5) in patients without comorbid depression or other anxiety disorders. Because of the high risk of adverse reactions and toxicity, barbiturates, antipsychotics, antipsychotic–antidepressant combinations, and antihistamines generally are not indicated in the treatment of GAD.[3] It is important to note that the benzodiazepines are more effective in treating the somatic and autonomic symptoms of GAD as opposed to the psychological symptoms (eg, apprehension and worry), which are reduced by antidepressants.[3]

TABLE 90-5

Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder

Medication	Brand Name	Initial Dose	Usual Range (mg/day)[a]	Comments
Antidepressants				
Duloxetine	Cymbalta	30 or 60 mg/day	60-120	FDA-approved; available generically
Escitalopram	Lexapro	10 mg/day	10-20	FDA-approved; available generically
Imipramine	Tofranil	50 mg/day	75-200	Available generically
Paroxetine	Paxil	20 mg/day	20-50	FDA-approved; available generically; avoid in pregnancy
	Pexeva			
Sertraline	Zoloft	50 mg/day	50-200	Available generically
Venlafaxine XR	Effexor XR	37.5 or 75 mg/day	75-225[b]	FDA-approved; available generically
Vilazodone	Viibryd	10 mg/day	20-40[b]	During concomitant use of a strong CYP3A4 inhibitor (eg, itraconazole, clarithromycin, voriconazole), dose should not exceed 20 mg once daily
Vortioxetine	Trintellix	5 mg/day	5-20	
Azapirone				
Buspirone	BuSpar	7.5 mg twice daily	15-60[b]	FDA-approved; available generically
Diphenylmethane				
Hydroxyzine	Vistaril	25 or 50 mg four times daily	200-400	FDA-approved; approved in children for anxiety and tension in divided daily doses of 50-100 mg; available generically
Antiseizure Medications				
Pregabalin	Lyrica	50 mg three times daily	150-600	Dosage adjustment required in renal impairment; available generically
Second-generation antipsychotic				
Quetiapine XR	Seroquel XR	50 mg at bedtime	150-300	Available generically

XR, extended-release.

[a]Older adult patients are usually treated with approximately one-half of the dose listed.

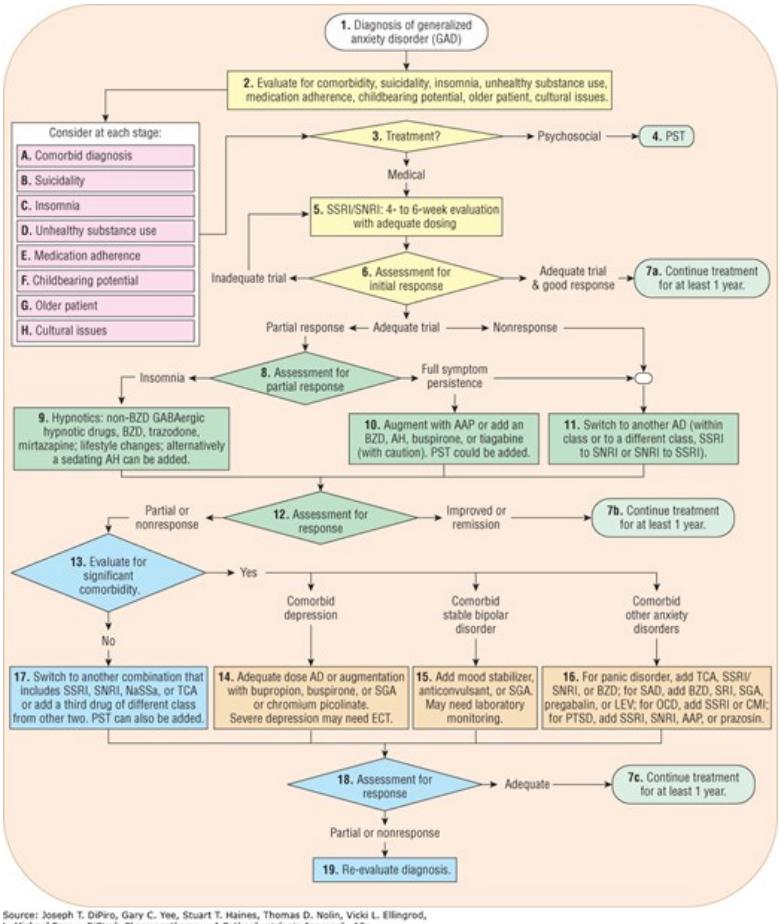
[b]No dosage adjustment is required in older adult patients.

Data from References 3 and 27-34.

The most recent evidence-based treatment guidelines come from the World Federation of Societies of Biological Psychiatry, the National Institute for Health and Clinical Evidence, and British Association for Psychopharmacology.[3,21,22] A descriptive flowchart with recommendations based on levels of evidence from the International Psychopharmacology Algorithm Project for the psychosocial and pharmacologic management of GAD is shown in Fig. 90-1.[35]

FIGURE 90-1

International Psychopharmacology Algorithm Project (IPAP) generalized anxiety disorder (GAD) algorithm flowchart. Yellow, first-line treatment (nodes 2, 3, 5, 6); green, second-line treatment (nodes 8-12); blue, third-line treatment, no comorbidity (nodes 13, 17, 18, 19); orange, third-line treatment, with comorbidity (nodes 14-16); light green, assessment and evaluation. Levels of evidence used in development of the flowchart were: 1, more than one placebo-controlled trial with sample sizes over 30; 2, one placebo-controlled trial (or active vs active medication comparison) with sample size of 30 or greater; 3, one or small ($n < 30$) placebo-controlled trial; 4, case reports or open-label trials; and 5, expert consensus without published evidence. (AD, antidepressant; AH, antihistamine; BZD, benzodiazepine; CMI, clomipramine; ECT, electroconvulsive therapy; GAD, generalized anxiety disorder; LEV, levetiracetam; NaSSa, noradrenergic and selective serotonergic antidepressant; PST, psychosocial treatment; SAD, social anxiety disorder; SGA, second-generation antipsychotic; SNRI, serotonin-norepinephrine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.) *(Reprinted from The International Psychopharmacology Algorithm Project. IPAP–Generalized Anxiety Disorder Algorithm. http://www.ipap.org/gad/index.php. Accessed November 11, 2021.)*



Antidepressant Therapy

3 Antidepressants are considered first-line agents in the management of GAD. Venlafaxine extended-release, duloxetine, paroxetine, and escitalopram are all FDA-approved antidepressants for GAD (see Table 90-5). Imipramine is considered a second-line agent, despite its efficacy, because of higher toxicity and adverse effect rates.[3]

4 The antianxiety response of antidepressants is delayed by 2 to 4 weeks or longer.[3,17] The pharmacology, pharmacokinetics, and medications interactions of the antidepressants are reviewed in Chapter 88, "Depressive Disorders."

Efficacy

Antidepressants are effective in the acute and long-term management of GAD. Data support the use of the SSRIs (eg, escitalopram, paroxetine, sertraline), and the serotonin–norepinephrine reuptake inhibitors (SNRIs) (eg, venlafaxine extended-release and duloxetine), for acute therapy (8- to 12-week trials) with response rates between 60% and 68%, and remission rates of approximately 30%.[3,21] Venlafaxine, escitalopram, paroxetine, duloxetine, and quetiapine may be the most likely to achieve remission of GAD symptoms; however, sertraline was the best tolerated.[36]

Mechanism of Action

The mechanism of action for antidepressants in anxiety disorders is not fully understood. Antidepressants may modulate receptor activation of neuronal signal transduction pathways connected to the neurotransmitters 5-HT, DA, and NE. In an animal model of anxiety, a number of candidate genes were identified that were normalized by fluoxetine treatment selectively in the hypothalamus.[37] By activating stress-adapting pathways, SSRIs and SNRIs reduce the somatic anxiety symptoms and the general distress experienced by patients.

Adverse Medication Reactions

The adverse reactions of medications used to treat anxiety disorders are provided in Table 90-6. In general, SSRIs and SNRIs are well tolerated, with GI adverse medication reactions and sleep disturbances being the most commonly reported. Headaches and diaphoresis occur early in treatment and are often transient, whereas weight gain and sexual dysfunction may continue in long-term treatment. The use of tricyclic antidepressants (TCAs) in clinical practice is limited by troublesome adverse reactions (eg, sedation, anticholinergic effects, and weight gain) in some patients as well as the risk of toxicity in overdose.

TABLE 90-6

Monitoring of Adverse Reactions Associated with Medications Used for Anxiety Disorders

Medication Class/Medication	Adverse Medication Reaction	Monitoring Parameter	Comments
SSRIs			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Nausea, diarrhea	Patient interview	Typically transient
	Headache	Patient interview	Typically transient
	Weight gain	Body weight, BMI, waist circumference	Paroxetine may be more likely to cause weight gain
	Sexual dysfunction	Patient interview	Significant reason for nonadherence

	Hyponatremia	Basic metabolic panel	Monitor at baseline and periodically thereafter. More frequent monitoring required in high-risk groups, especially older adults (>65 years)
	Thrombocytopenia	Complete blood count	Reported with citalopram
	Teratogenicity	Pregnancy test at baseline	Avoid paroxetine in pregnancy
	QT prolongation	ECG	Before starting citalopram, consider ECG and measurement of QT interval in patients with cardiac disease
	Discontinuation syndrome	Patient interview	Avoid abrupt discontinuation in all but fluoxetine
SNRIs			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Nausea, diarrhea	Patient interview	Typically transient
	Headache	Patient interview	Typically transient
	Elevated blood pressure	Blood pressure	Monitor blood pressure on initiation and regularly during treatment
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Discontinuation syndrome	Patient interview	Avoid abrupt discontinuation
TCAs			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Anticholinergic effects	Patient interview	Contraindicated with narrow-angle glaucoma, prostatic hypertrophy, and urinary retention
	Weight gain	Body weight, BMI, waist circumference	
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Sedation	Patient interview	Administer dosage at bedtime when feasible
	Arrhythmia	ECG	At baseline and periodically in children and patients >40 years of age

	Orthostatic hypotension	Blood pressure with position changes	
	Cholinergic rebound	Patient interview	Avoid abrupt discontinuation; taper doses
Benzodiazepines			
	Drowsiness, fatigue	Patient interview	Avoid operating large machinery; tolerance to sedation develops after repeated dosing
	Anterograde amnesia and memory impairment	Patient interview	Risk of anterograde amnesia is worsened with concomitant intake of alcohol
	Use disorder	Patient interview; prescription monitoring program	Monitor for early refills or escalation of dosage
	Withdrawal symptoms	Physical examination; patient interview	Taper doses on discontinuation
	Respiratory depression	Respiratory rate	Avoid administering with other CNS depressants (ie, opioids, alcohol)
	Psychomotor impairment	Physical examination	Increased risk of falls
	Paradoxical disinhibition	Physical examination; family report	Increase in anxiety, irritability, or agitation may be seen in older adults or children
Other Medications			
Buspirone	Nausea, abdominal pain	Patient interview	Typically transient
	Drowsiness, dizziness	Patient interview	Typically transient
Phenelzine	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Hypertensive crisis	Blood pressure	Tyramine-free diet and avoidance of medications interactions required
	Orthostatic hypotension	Blood pressure with position changes	
Pregabalin	Dizziness, somnolence	Patient interview	
	Peripheral edema	Physical examination	

	Thrombocytopenia	Complete blood count	
	Weight gain	Body weight	
Quetiapine	Sedation	Patient interview	
	Metabolic syndrome	Body weight, BMI, waist circumference, fasting lipids and glucose	Fasting labs at baseline and then periodically
	Akathisia	Patient interview	
	Tardive dyskinesia	Abnormal Involuntary Movement Scale	
	Orthostatic hypotension	Blood pressure with position changes	

BMI, body mass index; ECG, electrocardiogram; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Dosing and Administration

The antidepressants can be dosed once daily (see Table 90-5). Importantly, most patients require small initial daily doses for the first week or so of therapy to limit the development of transient increased anxiety, also known as jitteriness syndrome. The dose should then be slowly titrated to effect in order to reduce the occurrence of this excess anxiety. Patient education on this particular point in starting medications is critical to assure early treatment discontinuation does not occur, as this increase in anxiety will dissipate with time and a slow titration regimen.

Benzodiazepine Therapy

Although all benzodiazepines possess anxiolytic properties, only seven of the currently marketed agents have FDA approval for the treatment of GAD (see Table 90-4) as estazolam, flurazepam, temazepam, quazepam, and triazolam are marketed as sedative–hypnotic agents. Clonazepam is marketed as an antipanic agent and an antiseizure medication,[38] and midazolam and remimazolam are labeled for preoperative sedation. Alprazolam is indicated for the treatment of panic disorder with or without agoraphobia, as well as GAD.[39] Clobazam is indicated for adjunctive treatment of seizures in Lennox–Gastaut syndrome.[26]

Pharmacology and Mechanism of Action

The GABA-receptor model of anxiety theorizes that benzodiazepines ameliorate anxiety through potentiation of the inhibitory activity of GABA.[40] Pharmacologically benzodiazepines bind on the $GABA_A$ receptor at the α_1, α_2, α_3, and α_5 subunits in combination with a β subunit and the γ_2 subunit.[41] The anxiolytic effects of benzodiazepines are mediated at the α_2 site, while sedative effects result from binding at the α_1 subunit. The binding sites of GABA and benzodiazepines are at the receptor interfaces of α/β and α/γ_2, respectively. The GABA receptor controls tonic inhibition to reduce neuronal excitability[40]; however, other neurotransmitters (eg, 5-HT, NE, and DA) may also be involved in benzodiazepine activity.

Pharmacokinetics

Wide differences in milligram potency exist between the benzodiazepines; however, when appropriately dosed, all agents have similar anxiolytic and sedative–hypnotic activity. The variations in lipid solubility between compounds influence their pharmacokinetic properties. Knowledge of the different pharmacokinetic and pharmacodynamic properties can assist in choosing an appropriate anxiolytic (Table 90-7). After a single dose, the

onset, intensity, and duration of pharmacologic effects are important factors to consider when using benzodiazepines for the short-term, intermittent, or as-needed treatment of anxiety. Knowledge of a medication's pharmacokinetic properties, along with specific factors such as metabolic pathways (including active metabolites), lipophilicity, and protein binding can aid in selecting therapy.

TABLE 90-7

Pharmacokinetics of Benzodiazepine Antianxiety Agents

Medication	Time to Peak Plasma Level (Hours)	Elimination Half-Life, Parent (Hours)	Metabolic Pathway	Clinically Significant Metabolites	Protein Binding (%)
Alprazolam	1-2	12-15	Oxidation	—	80
Chlordiazepoxide	1-4	5-30	*N*-Dealkylation	Desmethyl chlordiazepoxide	96
			Oxidation	Demoxepam	
				DMDZ[a]	
Clonazepam	1-4	30-40	Nitroreduction	—	85
Clorazepate	1-2	Promedication	Oxidation	DMDZ	97
Diazepam	0.5-2	20-80	Oxidation	DMDZ	98
				Oxazepam	
Lorazepam	2-4	10-20	Conjugation	—	85
Oxazepam	2-4	5-20	Conjugation	—	97

[a]Desmethyldiazepam (DMDZ) half-life 50-100 hours.

Data from References 26 and 41.

The primary determinant of a medication's onset of effect after a single oral dose is the rate of absorption. Because of high lipophilicity, diazepam and clorazepate are absorbed rapidly and distributed quickly into the CNS. Therefore, the onset of anxiolytic effect occurs within 30 to 60 minutes, which results in a rapid and intense relief of anxiety. High lipophilicity also increases the extent of medication redistribution into the periphery, particularly adipose tissue, resulting in a shorter duration of effect after a single dose than is suggested by single-dose elimination half-life studies.[41] Clinically, patients can perceive a rapid onset of action, or "rush," which can be euphoric and contribute to misuse, while others may experience an unpleasant feeling of drowsiness or loss of control.

Compared with diazepam, lorazepam and oxazepam are relatively less lipophilic and have a slower absorption and onset of effect. These benzodiazepines have smaller volumes of distribution and a resulting longer duration of action.[41]

Parenteral administration via the intramuscular route should be avoided with diazepam secondary to variability in the rate and extent of medication absorption. Intramuscular lorazepam provides rapid, reliable, and complete absorption.

After multiple dosing, the rate and extent of medication accumulation are functions of the medication's elimination half-life in relation to dosing intervals, clearance, and formation of active metabolites. Differences in clinical effects that occur during and after repeated dosages are related in part

to variability in metabolism and metabolite accumulation.[41]

The benzodiazepines undergo two primary metabolic processes, hepatic oxidation (catalyzed by mainly cytochrome P450 [CYP] 3A4/5, as well as CYP2C19) and glucuronide conjugation. With the exception of lorazepam and oxazepam (which are conjugated only) and clonazepam (which undergoes nitroreduction through N-acetyltransferase-2 [NAT2]), all benzodiazepines are oxidized first and then conjugated and excreted renally.[42] Diazepam's metabolism specifically is also catalyzed by CYP2C19. Oxidation can be impaired in patients with liver disease, in older adults, and in those who simultaneously use medications that inhibit oxidation resulting in higher levels of the parent medication and/or an active metabolite.

Many benzodiazepines are converted to desmethyldiazepam (DMDZ), an active metabolite with a long elimination half-life (see Table 90-7) which is further oxidized to oxazepam and then conjugated and excreted. After multiple dosing, accumulation of DMDZ occurs, therapeutically providing a long-lasting antianxiety effect. Furthermore, if oxidation of DMDZ is impaired, its half-life is prolonged, and further medication accumulation can result with repeated dosing.

Clorazepate is a promedication and possesses no anxiolytic effects until metabolized to DMDZ. Before absorption, clorazepate is metabolized rapidly in the stomach through a pH-dependent process under acidic conditions.

Benzodiazepines with shorter half-lives (eg, alprazolam, lorazepam, and oxazepam) reach steady-state plasma concentrations rapidly, and accumulation after repeated dosing is minimal. Oxazepam and lorazepam have no active metabolites.

Benzodiazepine protein binding is extensive, especially for the agents with a long elimination half-life. After a single dose of a benzodiazepine with a long elimination half-life, the expected duration of clinical activity may not parallel the medication's pharmacokinetic half-life because of medication redistribution.[41] After multiple dosing, medications with long elimination half-lives and active metabolites require 1 to 2 weeks to reach steady state.

Efficacy

In clinical trials of benzodiazepines, 65% to 75% of patients with GAD showed a marked to moderate response, with most of the improvement occurring in the first 2 weeks of therapy.[21,22] Benzodiazepines are more effective on the somatic symptoms of anxiety and fail to obviate the cognitive or psychological symptoms (eg, worry) as mentioned previously.

Adverse Medication Reactions

The most common adverse reactions associated with benzodiazepine therapy involve CNS depression (see Table 90-6). This is manifested clinically as drowsiness, sedation, psychomotor impairment, and ataxia.[43] A transient mild drowsiness is experienced commonly by patients during the first few days of treatment; however, tolerance often develops. Disorientation, depression, confusion, irritability, aggression, and excitement are reported.[42]

Impairment of memory and recall also can occur during benzodiazepine treatment. The memory loss induced typically is limited to events occurring after medication ingestion (anterograde amnesia).[42] Anterograde amnesia is secondary to disordered consolidation processes that store information and is not impairment in the perception or retrieval of information.[3] Benzodiazepines with high affinity for binding to the benzodiazepine receptor (eg, alprazolam) appear to possess a higher potential for amnesia.[42]

Physical Dependence, Withdrawal, and Tolerance

Two serious complications of benzodiazepine therapy are the potential for unhealthy use and development of physical dependence. Benzodiazepine misuse is rare in the general population; however, individuals with a history of multiple substance use (eg, alcohol or sedatives) are at the greatest risk for developing a sedative, hypnotic, or anxiolytic use disorder.[42]

Because of the chronicity of illness, persons with GAD and panic disorder are at high risk of developing physical dependence to benzodiazepines which is a physiologic phenomenon demonstrated by the appearance of a predictable abstinence syndrome (withdrawal symptoms) on abrupt discontinuation of therapy.[42,43] Withdrawal symptoms can result because of the sudden dissociation of a benzodiazepine from its receptor site. After abrupt discontinuation, an acute decrease in GABA neurotransmission results, producing a less inhibited CNS.

Benzodiazepine Discontinuation

After benzodiazepine therapy is discontinued suddenly, several events can occur. Rebound anxiety represents an immediate, but transient return of original symptoms, at an increased intensity compared with baseline. In contrast, anxiety recurrence or relapse is the return of original symptoms with similar intensity as before treatment.

Withdrawal symptoms are the emergence of new symptoms and a worsening of preexisting symptoms after benzodiazepine discontinuation. Symptoms can persist for days to weeks and resolve gradually over months. In some patients it may be difficult to distinguish benzodiazepine withdrawal or rebound symptoms from the recurrence, or relapse of the underlying anxiety disorder.

Common symptoms of benzodiazepine withdrawal include anxiety, insomnia, restlessness, muscle tension, and irritability. Less frequently occurring symptoms are nausea, malaise, coryza, blurred vision, diaphoresis, nightmares, depression, hyperreflexia, and ataxia. Tinnitus, confusion, paranoid delusions, hallucinations, and seizures occur rarely. Withdrawal seizures typically occur approximately 1 week after discontinuation for agents with a long elimination half-life. For agents with a short elimination half-life, withdrawal seizures can occur with both therapeutic and high doses of benzodiazepines use and usually within 3 days of medication discontinuation. Each patient who has abruptly stopped a benzodiazepine or has experienced seizures should be individually approached because high benzodiazepine doses, a long duration of therapy, and concurrent ingestion of substances or medications that lower the seizure threshold are all risk factors.

Furthermore, similar to withdrawal seizures, the onset of generalized withdrawal symptoms in patients ingesting benzodiazepines with short elimination half-lives occurs much earlier (within 24-48 hours) than in those taking benzodiazepines with long elimination half-lives (within 3-8 days). Other factors associated with an increased incidence and severity of benzodiazepine withdrawal include high doses and long-term benzodiazepine therapy.[42,43]

A strategy to minimize the severity of benzodiazepine withdrawal is a 25% dosage reduction per week if therapy had exceeded 8 weeks.[43] The rate can be decreased to 25% every 2 weeks if withdrawal symptoms emerge near the end of the dosage taper. Long-term use of benzodiazepines (ie, 1 year or longer) requires a 2- to 4-month slow taper. Tapering will not eliminate the emergence of withdrawal symptoms entirely but will prevent severe withdrawal. Slow medication taper is extremely important for the medications with a short elimination half-life because some individuals have greater difficulty with discontinuation. Withdrawal symptoms with short half-life benzodiazepines were no more severe than with longer half-life agents; therefore, switching from a short- to long-acting benzodiazepine before gradual taper is not supported. Adjunctive use of pregabalin can help reduce withdrawal severity during the benzodiazepine taper.[44] A combination of psychotherapy interventions (including CBT) with tapering protocols resulted in superior discontinuation outcomes.[45] Patients should avoid the intake of alcohol and stimulants during the withdrawal process. Although tolerance develops to the sedative, muscle relaxant, and antiseizure activities, the benzodiazepines do not appear to lose anxiolytic or antipanic efficacy. However, the anxiolytic efficacy of benzodiazepines in long-term clinical trials (greater than 6-8 months of chronic use) has not been documented.[3,21,22]

Medication Interactions

Medication interactions with the benzodiazepines generally fall into two categories: pharmacodynamic and pharmacokinetic. Simultaneous use of alcohol and a benzodiazepine results in additive CNS depressant effects. In addition, concurrent use of a benzodiazepine and other medications/substances with CNS depressant properties (eg, opioids, antipsychotics, and antihistamines) can potentiate the adverse sedative effects. When ingested alone in an overdose attempt, benzodiazepines are rarely life-threatening. However, the combination of benzodiazepines with alcohol or other CNS depressant agents is potentially fatal.

Concurrent use of medications that inhibit CYP3A4 (eg, ketoconazole, nefazodone, and ritonavir) can increase the blood levels of alprazolam and diazepam. Medications that induce cytochrome CYP3A4 (eg, carbamazepine, St. John's wort) can reduce benzodiazepine levels. Medications that inhibit or induce CYP2C19 (eg, fluoxetine, fluvoxamine, omeprazole) or *N*-acetyltransferase 2 activity can alter diazepam and clonazepam metabolism, respectively. Consult a medications interaction website (http://www.factsandcomparisons.com/facts-comparisons-online.aspx) for further information.

Dosing and Administration

Benzodiazepine dosage requirements vary widely among patients and must be individualized. Therapy should be initiated using low doses (eg, alprazolam 0.25 mg three times a day or equivalent doses of other benzodiazepines) and titrated upward to relieve anxiety symptoms and avoid adverse events. After an initial treatment response is achieved, agents with long elimination half-lives can be dosed at bedtime. Dosage adjustments should be made weekly. Three to 4 weeks of a daily dose at the maximum dose constitutes an adequate clinical trial (see Table 90-4).[2,21,22]

The duration of benzodiazepine therapy for the acute management of anxiety should be limited to 2 to 4 weeks. In general, benzodiazepines should be used with a regular dosing regimen and not on an as-needed basis when used for the treatment of an anxiety disorder.[3] Only in the treatment of short-term distress (eg, air travel, dental phobia) as-needed use may be justified.[3] Individuals with persistent symptoms should be managed with antidepressants because of the risk of dependence with continued benzodiazepine therapy.

Patient education should include the anticipated length of medication therapy, potential adverse reactions, and consequences of the ingestion of alcohol and other CNS depressants. Patients should understand that benzodiazepines provide symptomatic relief but do not solve underlying psychological problems. Patients should be instructed not to decrease or discontinue benzodiazepine usage without contacting their prescriber.

Buspirone Therapy

Buspirone is a nonbenzodiazepine anxiolytic that lacks antiseizure, muscle relaxant, hypnotic, motor impairment, and physical dependence properties. It is considered to be a second-line agent for GAD because of inconsistent reports of efficacy (particularly long term), delayed onset of effect (ie, 2 weeks or longer), and lack of efficacy for other potential, concurrent, depressive, and anxiety disorders.[2] Unlike benzodiazepines, buspirone is effective for the psychological symptoms of anxiety.[2]

Pharmacology and Mechanism of Action

Buspirone's anxiolytic mechanism of action is unknown. It may exert its anxiolytic effect through partial agonist activity at the 5-HT_{1A} presynaptic receptors, thus reducing the firing of 5-HT neurons.[41]

Pharmacokinetics

After an oral dose, buspirone is absorbed rapidly and completely, and undergoes extensive first-pass metabolism. The mean elimination half-life is 2.5 hours, and it must be dosed two to three times daily, which adversely affects medication adherence.[41]

Adverse Medication Reactions

Includes dizziness, nausea, and headaches[41] (see Table 90-6).

Interactions

Medications that inhibit CYP3A4 (eg, verapamil, itraconazole, fluvoxamine) can increase buspirone levels, and rifampin caused a 10-fold reduction in buspirone levels. Buspirone reportedly elevates blood pressure in patients taking a monoamine oxidase inhibitor (MAOI).

Dosing and Administration

The dose of buspirone can be titrated in increments of 5 mg/day every 2 to 3 days as needed.[41] The onset of improvement in psychological symptoms precedes the relief of somatic symptoms; maximum therapeutic benefit might not be evident for 4 to 6 weeks.

Buspirone is a treatment option for patients with GAD, particularly for those with uncomplicated GAD, in patients who fail other anxiolytic therapies, or in patients with SUDs. It is not useful in clinical situations requiring immediate anxiolysis or for situations requiring as-needed anxiolytic therapy.[41] Buspirone may have less efficacy in patients who have previously used benzodiazepines, as it does not provide the same rapid relief of symptoms.[2]

Alternative Medication Treatments

Hydroxyzine, pregabalin, and second-generation antipsychotics (SGAs) are alternative treatments in GAD.[21,27] The effectiveness of hydroxyzine as an antianxiety agent for long-term use (ie, more than 4 months) has not been assessed by systematic clinical studies.[34] Hydroxyzine is commonly used in the primary care setting, but it is considered to be a second-line agent because of adverse medication reactions and lack of efficacy for comorbid disorders.[3] Pregabalin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels to reduce nerve terminal calcium influx and acts on "hyperexcited" neurons. The anxiolytic effects produced by pregabalin compare to lorazepam and alprazolam with fewer dropouts in acute efficacy trials.[46] Quetiapine extended-release 150 mg/day monotherapy was superior to placebo in three studies and was as effective as paroxetine 20 mg/day and escitalopram 10 mg/day but with an earlier onset of action.[27] In a 52-week treatment of GAD, quetiapine extended-release was superior to placebo in the prevention of anxiety relapse.[27] Notably, quetiapine is not FDA-approved for GAD, and the long-term risks and benefits of SGAs in the treatment of GAD are unclear.[27] Despite some evidence of efficacy, support for the use of kava kava for GAD has been blunted by ongoing safety concerns following numerous reports of liver toxicity.[47] Although valerian, St. John's wort, and passionflower have been used to manage GAD, there is insufficient evidence of their effectiveness and safety.[47]

Special Populations

The management of anxiety in patients with SUDs, pregnant individuals, children, older adult patients, and those patients with adherence problems requires special consideration in the choice of anxiolytic. Patients with GAD may use alcohol, cannabis, or other substances to manage anxiety. The symptoms of GAD are similar to those of withdrawal, and it is difficult to confirm the diagnosis of GAD until after abstinence is obtained; therefore, benzodiazepine therapy should be avoided in this population if possible.

Pregnancy

Anxiety that occurs during pregnancy and the postpartum period potentially may pose significant risk to the child. Clinical practice guidelines for anxiety disorders recommend use of fluoxetine, sertraline, or citalopram; however, jitteriness, myoclonus, and irritability in the neonate and premature infant have been reported.[48] Paroxetine should be avoided in pregnant individuals because of risk of cardiovascular malformations.[30]

Cleft lip, cleft palate, and other teratogenic effects are associated with benzodiazepine use, but a causal relationship is inconclusive. Clinicians should avoid benzodiazepine use during the first trimester or using the agent as monotherapy. In addition, efforts should be made to use the lowest dosage for the shortest period of time and divide the total daily dosage into two or three doses to prevent high peak plasma levels.[48] Benzodiazepine risks for the child during the third trimester include sedation, withdrawal symptoms, and "floppy baby syndrome" (eg, hypotonia, low Apgar scores, hypothermia). Alprazolam should be avoided during pregnancy because of neonatal withdrawal. Should benzodiazepines be required during pregnancy, the preferred agents are diazepam and chlordiazepoxide[49]; however, the antidepressants are favored for GAD during pregnancy based on safety considerations. Diazepam and clonazepam should not be used by individuals providing human milk to infants due to risk of sedation, lethargy, and weight loss seen for the child.[49]

Children and Adolescents

There are few controlled clinical trials of medications in children and adolescents with GAD. Use of CBT alone or in conjunction with antidepressants can have long-term benefits.[50] Randomized controlled trials of fluvoxamine, fluoxetine, sertraline, duloxetine, and venlafaxine extended-release indicate short-term efficacy[50]; however, irritability and oppositional behavior was reported with clonazepam.[50] No antidepressant is FDA-indicated for GAD in children or adolescents. Increased monitoring for behavioral changes with benzodiazepines and suicide-related adverse effects with antidepressants is necessary if these agents are prescribed.

Hepatic Disease and Older Adult Patients

Patients with hepatic disease are at risk for medication accumulation and subsequent complications. In particular, duloxetine use should be avoided in patients with hepatic insufficiency.[28] Accumulation of benzodiazepines can result in older adults secondary to a decreased capacity for oxidation and alterations in the volume of distribution. Therefore, intermediate- or short-acting benzodiazepines without active metabolites are preferred for chronic use. Older adult patients are also sensitive to the CNS adverse medication reactions of benzodiazepines (regardless of half-life), and their use

is associated with a high frequency of falls and hip fractures. Recent studies of buspirone, duloxetine, escitalopram, sertraline, venlafaxine, and pregabalin showed efficacy in older adult patients with GAD.[2,51,52]

Evaluation of Therapeutic Outcomes

Initially, patients with GAD should be monitored once every 2 weeks for a reduction in the frequency, duration, and severity of anxiety symptoms and improvement in functioning.[2] The clinician should assess the patient for response to treatment by asking about specific target symptoms of anxiety and emergence of adverse events. Ideally, the patient should have no or minimal anxiety or depressive symptoms and no functional impairment. Use of an objective measurement of remission of GAD (eg, Hamilton Rating Scale for Anxiety score less than or equal to 7 and a Sheehan Disability Scale score less than or equal to 1 on each item) can assist in the evaluation of medication response.[2] The Generalized Anxiety Disorder 7-Item Scale is a patient-rated scale that can be used for screening and monitoring improvement of symptoms.[23] See Chapter e81, "Evaluation of Psychiatric Illness" for more information about assessments for anxiety disorders.

The definition of treatment resistance is defined as a poor, partial, or lack of response with at least two antidepressants from different classes. Treatment strategies for patients who do not achieve an appropriate response with a first-line agent include increasing the dose of the SSRI/SNRI, changing to a different agent in the same class, changing to a different agent from a different class, or augmentation of therapy. At any point of nonresponse or loss of previous response, the clinician should assess for (a) symptoms (eg, psychotic symptoms) that may suggest a need for additional medications or (b) reasons for treatment nonadherence (eg, adverse medication reactions, cost of medications, limited understanding of the illness or treatments). Patients should also be assessed for concurrent SUD, concurrent illnesses, and suicidal thoughts. Once a patient has responded to pharmacotherapy, the regimen should be continued for at least 1 year.[22,35] Early discontinuation is associated with a greater risk of relapse.[22]

TREATMENT—PANIC DISORDER

Desired Outcomes

The goal of therapy in panic disorder is remission. Patients should be free of panic attacks, have no or minimal anticipatory anxiety and agoraphobic avoidance, and have no functional impairment.[20]

General Approach

Therapeutic options include single or combined pharmacologic agents, concurrent psychotherapy, or psychotherapy followed by pharmacotherapy. Most patients without agoraphobic avoidance will improve with pharmacotherapy alone; however, if avoidance is present, CBT is typically initiated concurrently. With all effective pharmacotherapy, resolution of agoraphobic avoidance tends to occur slowly. A meta-analysis comparing the use of SSRIs and venlafaxine in panic disorder showed response to be similar among treatments.[53] Adding psychosocial treatment to pharmacotherapy may improve long-term outcomes by reducing the likelihood of relapse when pharmacotherapy is stopped.[20]

Considerations that guide selection of the treatment modality for panic disorder include patient preference, treatment history, the presence of co-occurring medical or other psychiatric conditions, cost, and treatment availability. Psychosocial treatment in the form of CBT is recommended for patients who prefer nonpharmacologic therapy and who are able to invest the effort and time to attend weekly sessions and between-session homework exercises. Pharmacotherapy with a first-line agent is recommended for patients who prefer medications or who do not have access to or resources to engage in CBT. Combination with psychotherapy and pharmacotherapy is appropriate for patients who have failed monotherapy with medication or CBT.

Providing education about the disorder may relieve some of the symptoms of panic by helping the patient to realize that the symptoms are neither life-threatening nor uncommon. Patients should be informed regarding the lag time before a therapeutic response will occur and any problematic adverse medication reactions that might affect early adherence or result in premature treatment discontinuation (eg, jitteriness syndrome). Many patients are reluctant to take medications for fear that their illness will worsen or that they will become physically dependent. Adverse events are often perceived as a worsening of the illness and can contribute to nonadherence or prevent necessary dosage increases. A strong therapeutic alliance between the clinician and the patient is important in supporting the patient through the aspects of the treatment that may provoke anxiety.

Nonpharmacologic Therapy

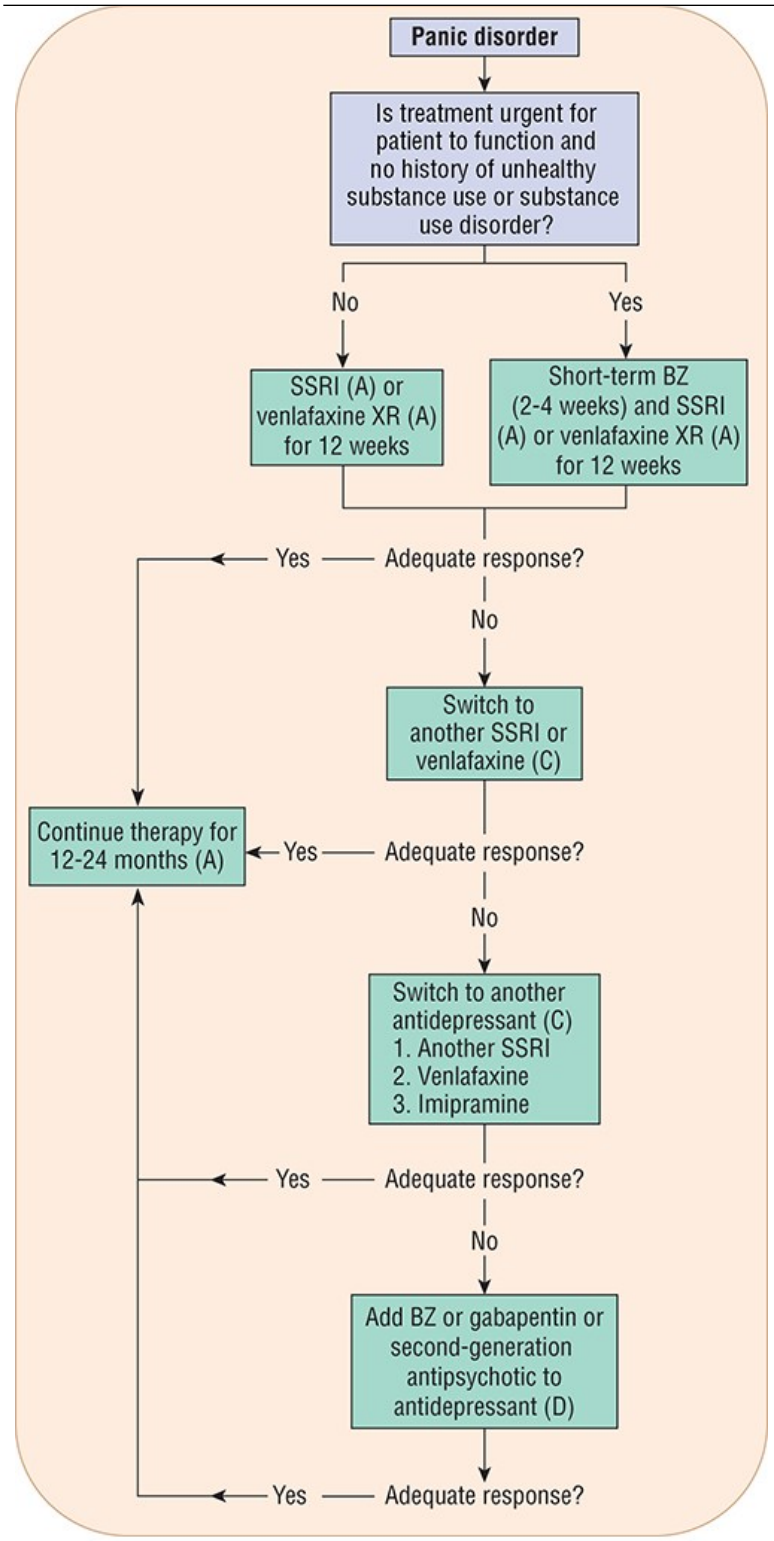
Patients should be educated to avoid agents that can precipitate panic attacks, including caffeine, nicotine, alcohol, other substances, and nonprescription stimulants.[1,20] Daily smoking increases risk for panic attacks and may be a causal or exacerbating factor in some individuals with panic disorder.[20] Aerobic exercise (eg, walking for 60 minutes or running for 20-30 minutes 4 day/week) may benefit patients with panic disorder.[22] Participation in CBT is associated with short-term improvement in 80% to 90% of patients and 6-month improvement in 75% of patients. A CBT course for panic disorder is 16 to 20 hours in length conducted over a period of 4 months.[22] Bibliotherapy (the use of self-help books), exercise, and Internet-based CBT are other options.[20]

Pharmacologic Therapy

Panic disorder is treated effectively with several medications including SSRIs, the SNRI venlafaxine, imipramine, and the benzodiazepines alprazolam and clonazepam[20,22] (Table 90-8). Alprazolam, clonazepam, fluoxetine, paroxetine, sertraline, and venlafaxine are all approved for this indication. In general, SSRIs are the first-line agents because of their tolerability and efficacy in acute and long-term studies[2,20]; however, the benzodiazepines are the most commonly used medications for panic disorder.[20] In a meta-analysis of the pharmacotherapy of panic disorder, the following antidepressants were significantly superior to placebo with the following *increasing* order of effectiveness: citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine for overall anxiety symptoms.[53] Imipramine is effective for panic disorder; however, it is considered to be a second-line agent because of the significant cardiovascular and anticholinergic adverse medication reactions associated with its use. Five practice guidelines are published,[2,3,20-22] and Fig. 90-2 is an algorithm for the pharmacologic therapy of panic disorder.

FIGURE 90-2

Algorithm for the pharmacotherapy of panic disorder. Strength of recommendations: A, directly based on category I evidence (ie, meta-analysis of randomized controlled trials [RCT] or at least one RCT); C, directly based on category III evidence (ie, nonexperimental descriptive studies); D, directly based on category IV evidence (ie, expert committee reports or opinions and/or clinical experience of respected authorities). (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.) *(Adapted from References 20 and 22.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 90-8

Medications Used in the Treatment of Panic Disorder

Class/Generic Name	Brand Name	Starting Dose	Antipanic Dosage Range (mg)	Comments
SSRIs				
Citalopram	Celexa	10 mg/day	20-40	Dosage used in clinical trials; maximum dose limited by QT prolongation; available generically
Escitalopram	Lexapro	5 mg/day	10-20	Dosage used in clinical trials; available generically
Fluoxetine	Prozac	5 mg/day	10-30	Available generically
Fluvoxamine	Luvox	25 mg/day	100-300	Available generically
Paroxetine	Paxil	10 mg/day	20-60	FDA-approved; available generically
	Pexeva			
	Paxil CR	12.5 mg/day	25-75	
Sertraline	Zoloft	25 mg/day	50-200	FDA-approved; available generically
SNRI				
Venlafaxine XR	Effexor XR	37.5 mg/day	75-225	FDA-approved; available generically
Benzodiazepines				
Alprazolam	Xanax	0.25 mg three times a day	4-10	FDA-approved; available generically
	Xanax XR	0.5-1 mg/day	1-10	
Clonazepam	Klonopin	0.25 mg once or twice per day	1-4	FDA-approved; available generically
Diazepam	Valium	2-5 mg three times a day	5-20	Dosage used in clinical trials; available generically
Lorazepam	Ativan	0.5-1 mg three times a day	2-8	Dosage used in clinical trials; available generically
TCA				
Imipramine	Tofranil	10 mg/day	75-250	Dosage used in clinical trials; available generically
MAOI				
Phenelzine	Nardil	15 mg/day	45-90	Dosage used in clinical trials; available generically

CR, controlled release; MAOI, monoamine oxidase inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; XR, extended-release.

Data from References 3,20, and 54.

Benzodiazepines are considered second-line agents, and because of the risk of physical dependence should be used only after several trials of antidepressants have failed.[2,20] Additionally because of the potential emergence of depressive symptoms during treatment, benzodiazepines should not be used as monotherapy in a patient who is clinically depressed or has a history of depression. The short-term (4-6 weeks) addition of alprazolam or clonazepam to antidepressants may produce a more rapid therapeutic response, with discontinuation of the benzodiazepine by week 7 of therapy.[2] However, in patients whose illness is complicated by a history of alcohol or unhealthy substance use, benzodiazepine use should be avoided.[20]

Selective Serotonin Reuptake Inhibitors

Efficacy

All SSRIs may be effective in panic disorder.[20] The percentage of patients who become panic-free ranges between 60% and 80%.[20] The antipanic effect of SSRIs is delayed for at least 4 weeks, and some patients do not respond for 8 to 12 weeks.[20]

Adverse Medication Reactions

Typical antidepressant doses of SSRIs can cause insomnia, jitteriness, restlessness, and agitation, and lead to medication discontinuation in patients with panic disorder, similar to the effects previously described. Table 90-6 includes additional adverse medication reactions associated with SSRI use in panic disorder.

Dosing and Administration

Low initial doses of SSRIs are recommended (see Table 90-8) to avoid stimulatory adverse medication reactions (eg, insomnia or nervousness), and should be maintained for the first week of therapy. However, doses at the upper end of the dosing range can be necessary to achieve response after careful titration.[22,54]

Serotonin–Norepinephrine Reuptake Inhibitors

Efficacy

Venlafaxine extended-release 75 to 150 mg/day is superior to placebo in the proportion of patients becoming free from full-symptom panic attacks. Other data support the efficacy of venlafaxine in reducing the severity of anticipatory anxiety, fear, and avoidance.[54] Venlafaxine is similar in efficacy to paroxetine in patients with panic disorder and superior to placebo in a relapse prevention study.[54]

Adverse Medication Reactions

The most common for venlafaxine extended-release in clinical trials of panic disorder were nausea, dry mouth, constipation, anorexia, insomnia, somnolence, tremors, sweating, and sexual dysfunction.[20]

Dosing and Administration

The dosage of venlafaxine extended-release is 37.5 mg/day for the first 3 to 7 days, and then increased to a minimum of 75 mg/day (Table 90-8). Increasing the dose to 150 mg/day after initial nonresponse or partial response is recommended. A dose-response relationship was not evident in clinical trials.[31]

Tricyclic Antidepressants

Efficacy

Imipramine is the most studied TCA, alleviating panic attacks in 75% of patients. It effectively blocks panic attacks within at least 4 weeks. However, maximal improvement (including antiphobic response) does not occur until 8 to 12 weeks.[20]

Adverse Medication Reactions

See Table 90-6. Up to 40% of patients experience stimulant-like effects, including anxiety, insomnia, and jitteriness.[20] These adverse medication reactions often affect patient adherence, result in premature treatment discontinuation, prevent medication dosage increases, and interfere with the overall treatment outcome.

Other problems with TCA use in panic disorder are well documented and include anticholinergic effects, orthostatic hypotension, delayed onset of antipanic effects, and toxicity in overdose.[20] Approximately 25% of patients reportedly discontinue treatment because of adverse medication reactions, especially weight gain.[20]

Dosing and Administration

When using imipramine, treatment should be slowly increased by 10 mg every 2 to 4 days as tolerated (Table 90-8).

Benzodiazepines

Efficacy

The high-potency benzodiazepines clonazepam and alprazolam are the preferred agents for the treatment of panic disorder.[20,22] Alprazolam provides rapid relief for patients in distress, but because of its short half-life, multiple daily dosing is required and often results in profound withdrawal symptoms with missed doses.[20] Additionally diazepam and lorazepam, when taken in sufficiently high doses, are possibly effective in treating panic disorder.[20] Therapeutic response to benzodiazepines occurs in 1 to 2 weeks, and relapse rates of 50% or higher are common despite slow medication tapering during discontinuation of therapy.[43]

Adverse Medication Reactions

Patient acceptance of benzodiazepines is usually not a problem, and except for sedation, adverse medication reactions are rarely reported (see Table 90-6).

Dosing and Administration

Doses of clonazepam can be increased by 0.25 or 0.5 mg every 3 days to 4 mg/day if needed,[39] and alprazolam can be slowly increased over several weeks to reach an ideal dose. The duration of action of immediate-release alprazolam can be as little as 4 to 6 hours which may result in breakthrough symptoms; use of the extended-release alprazolam or clonazepam will avoid this problem. Most patients require 3 to 6 mg/day of alprazolam, and some need higher doses to obtain a full therapeutic (antipanic and antiphobic) response.

Alternative Medication Treatments

Buspirone, trazodone, bupropion, antipsychotics, antihistamines, and β-blockers are ineffective in panic disorder.[2,3,20-22] The majority of studies assessing the efficacy of MAOIs in treating panic disorder were open-labeled and lacked adequate sample sizes. Therefore, MAOIs are reserved for the most refractory or difficult patients.[20]

Phases of Therapy

Acute Phase

The main goal of therapy in the acute phase is reduction of symptoms (eg, resolution of panic attacks, reduction in anxiety and phobic fears, resumption of the patient's usual activities).[20,21] The duration of this phase is generally 1 to 3 months depending on the choice of medication. Therapy

should be altered if there is no response after 6 to 8 weeks of an adequate dose.

The guiding principle for SSRIs and SNRIs in panic disorder is to start with low doses (approximately one-fourth to one-half of the starting doses for depression), use an adequate dose, and treat for about 12 weeks.[20,21] Adverse medication reactions, often from too high an initial dose, can prevent achievement of an optimal dosage, compromise treatment response, contribute to patient nonadherence, and lead to premature treatment discontinuation.

The duration of the acute phase with benzodiazepines is approximately 1 month because response is rapid. A regular dosing schedule rather than an "as-needed" schedule is preferred for patients with panic disorder who are taking benzodiazepines, where the goal is to prevent panic attacks rather than reduce symptoms once an attack has already occurred.[20]

Maintenance Phase and Discontinuation

6 The optimal length of therapy is unknown; however, the total duration of therapy appears to be 12 to 24 months before medication discontinuation over 4 to 6 months is attempted.[20] The dose used in the acute phase is continued into the maintenance phase.[20] When medications are discontinued too early, a high rate of relapse occurs; thus, longer periods of treatment are associated with a more sustained response. Reinstitution of medication usually results in renewed clinical response.[20] Pharmacotherapy, even of a long duration, might not prevent relapse, and many patients require long-term maintenance therapy.

The most important determinant of adherence with maintenance therapy is the tolerability of adverse events.[20] Some adverse events that are experienced short term become unbearable during long-term management (eg, sexual dysfunction and weight gain). All TCAs, SSRIs (except fluoxetine), and venlafaxine can be associated with discontinuation symptoms, which can present as flu-like symptoms.

The primary risk of long-term benzodiazepine use is the development of physical dependence and withdrawal symptoms upon discontinuation. Misuse of benzodiazepines usually is confined to patients with a personal or family history of substance or alcohol use disorders.[43,44] The approach to benzodiazepine discontinuation involves a slow and gradual tapering of the dose because withdrawal symptoms and rebound anxiety may occur during discontinuation. Benzodiazepines should be tapered very slowly in patients with panic disorder over 2 to 4 months at rates no higher than 10% of the dose per week.[20,43] Patients receiving benzodiazepines and antidepressants should be told not to decrease or discontinue therapy unless authorized by their clinician.[20]

Treatment Refractory Symptoms

Common reasons for nonresponse to treatment are comorbid psychiatric disorders, rapid dosage increases with resulting intolerable adverse medication reactions, and underdosage.[20] All standard treatments should be tried before using augmentation strategies. In patients with a partial response to one agent, a low dose of another antipanic agent (eg, a TCA, benzodiazepine, or an SSRI) can be added.[20]

Special Populations

Older adult patients with panic disorder have fewer, less intense symptoms and avoidant behavior than younger patients.[20] Youth often present with fear that they are dying or being smothered, and agoraphobia can be manifested as a fear of leaving home.[1] Overall, CBT is effective in both populations. If pharmacotherapy is used, antidepressants, especially the SSRIs, are preferred for management of panic disorder, and benzodiazepines are second-line agents because of potential problems with disinhibition in these two populations. The course of panic disorder may be highly variable during pregnancy and the postpartum period. It is unclear whether uncontrolled symptoms of panic disorder affect the course or outcome of pregnancy.[20] Little evidence exists on the use of psychosocial interventions for individuals with panic disorder who are pregnant, lactating, or planning to become pregnant. Nonpharmacologic interventions should be considered as first-line treatment in these patients. Pharmacotherapy may also be indicated but requires careful evaluation of the potential benefits and risks.[20]

EVALUATION OF THERAPEUTIC OUTCOMES

During the first few weeks of the acute phase of therapy, patients with panic disorder should be seen every 1 to 2 weeks when starting a new medication, and then every 2 to 4 weeks to adjust medication dosages based on improvement in panic symptoms and to monitor for adverse events.[20,22] After the dose is stabilized and symptoms have decreased, visits every 2 months should suffice.[21] The patient should be counseled to maintain a diary to record the date, time, frequency, duration, and intensity of panic episodes, level of anticipatory anxiety or agoraphobic avoidance, and the severity of distress and impairment related to the panic disorder. Treatment outcomes can be assessed objectively by use of the Panic Disorder Severity Scale. Remission is defined as equal to or less than 3 with no or mild agoraphobic avoidance, anxiety, disability, or depressive symptoms. Treatment response is indicated by a 40% or greater reduction in overall score.[2]

At scheduled visits, the clinician can inquire about the level of disability experienced by the patient and have the patient complete the Sheehan Disability Scale (with a goal of less than or equal to 1 point on each item). See Chapter e81 for additional assessments that can be used to evaluate therapeutic outcomes for anxiety disorders. During medication discontinuation, the frequency of appointments should be increased to evaluate for emergence of potential withdrawal symptoms and monitor for relapse.

TREATMENT—SOCIAL ANXIETY DISORDER

Desired Outcomes

The goals of therapy in the acute phase of treatment are to reduce physiologic symptoms of anxiety (eg, tachycardia, flushing, and sweating), social anxiety, and phobic avoidance. The duration of this phase is 4 to 12 weeks, depending on the medication therapy.

The goals of therapy in the continuation phase (3-6 months) are to extend the therapeutic benefits, especially the patient's ability to participate in social activities, and improve QOL. Although the primary goal of treatment is to reduce anxiety symptoms to manageable levels, even modest reductions in avoidance and discomfort can be highly valued by patients.[18]

7 At least a 6- to 12-month medication maintenance period is recommended to maintain improvement and decrease the rate of relapse.[2,3,21] Situations suggesting a possible need for long-term treatment include the presence of unresolved symptoms or comorbidity, an early onset of disease, and a prior history of relapse.[18] The long-term goal in the treatment of SAD is remission with the disappearance of the core symptoms of social anxiety, little or no anxiety, and no functional impairment or concurrent depressive symptoms.[18,55]

General Approach

Patients with SAD should be identified early and treated aggressively.[18] Obstacles to effective treatment include patient avoidance of therapy secondary to fear and shame, treatment directed toward somatic symptoms or concurrent conditions, and financial barriers.[18] Patients with SAD often respond more slowly and less completely than patients with other anxiety disorders. Therefore, it is important to set reasonable expectations for response to therapy. Consideration of current symptoms, prior treatments, concurrent conditions, and history of SUD guides treatment selection.

Both CBT and pharmacotherapy are effective in the treatment of SAD.[2,18,55,56] Pharmacotherapy is often the most practical choice because CBT might not be available in medically underserved areas. Acute treatment outcomes for CBT and pharmacotherapy are equivalent.[2,3,18] Pharmacotherapy is superior in reducing subjective general anxiety acutely, although CBT has a greater likelihood of maintaining response after termination.[18,55,56]

There are no data to predict which patients will respond best to pharmacotherapy, CBT, or a combination, or maintain gains after discontinuing pharmacotherapy. The only significant indication of treatment response in pharmacotherapy is duration of treatment.[55-58] Some patients elect lifelong therapy, and many are reluctant to attempt medication discontinuation because of fear of relapse.

Despite the availability of effective treatments for social anxiety, most adults in the United States with social anxiety do not receive mental health care for their symptoms. Often the symptoms that patients desire to relieve interfere with the ability to seek treatment. Patients often feel embarrassed of what others might think or say about them. It is important to develop an alliance with the patient and offer reassurance throughout the treatment process.

Certain complications may influence the choice of first-line pharmacotherapy. Comorbid depression or suicidal ideation requires careful evaluation

and close monitoring. Patients with comorbid SUD on presentation may require postponing pharmacotherapy until after detoxification and avoidance of use of benzodiazepines as part of treatment.

Patient-specific education about treatment is important. Patients should be instructed about the gradual onset of effect, when to expect full therapeutic benefit, and that long-term therapy is required. When pharmacotherapy is discontinued, the dosage needs to be gradually decreased over several months, and the patient should be seen more frequently to monitor for signs and symptoms of relapse or withdrawal.

Although pharmacotherapy usually leads to improvement in social and occupational functioning, most patients do not achieve a full remission. Many patients require additional treatment, often in the form of CBT.

Nonpharmacologic Therapy

Patients should be educated about SAD and support groups. Self-help group programs that focus on effective communication can benefit people with anxiety involving public speaking. The peer-to-peer support groups provided by NAMI can be another resource for patients with SAD.

In general, CBT consists of exposure therapy, cognitive restructuring, relaxation training techniques, and social skills training.[2,3,18,21,56] Through CBT, patients learn to overcome anxiety in social situations and alter the beliefs and responses that maintain this anxiety, with therapy usually lasting several months and is often conducted in groups.[18,57]

Pharmacologic Therapy

Antidepressant Therapy

8 The SSRIs and venlafaxine are beneficial for patients with concurrent depression and are safe when used in patients with an SUD. Paroxetine, sertraline, fluvoxamine extended-release, and venlafaxine extended-release are approved for the treatment of SAD and are considered first-line agents because of efficacy and tolerability (Table 90-9). Controlled trials comparing different SSRIs, or SSRIs and an SNRI, demonstrated equivalent efficacy between agents.[55-57] The TCAs are not effective in SAD.[2,21] Evidence-based guidelines for the treatment of SAD were published by the Canadian Psychiatric Association, World Federation of Societies of Biological Psychiatry, the National Institute for Health and Care Excellence, and the British Association for Psychopharmacology.[2,3,18,21] An algorithm for the pharmacotherapy of SAD appears in Fig. 90-3.

FIGURE 90-3

Algorithm for the pharmacotherapy of social anxiety disorder. Strength of recommendations: A, directly based on category I evidence (ie, meta-analysis of randomized controlled trials [RCT] or at least one RCT); C, directly based on category III evidence (ie, nonexperimental descriptive studies); D, directly based on category IV evidence (ie, expert committee reports or opinions and/or clinical experience of respected authorities). SSRI, selective serotonin reuptake inhibitor. *(Adapted from References 2,3,21, and 55.)*

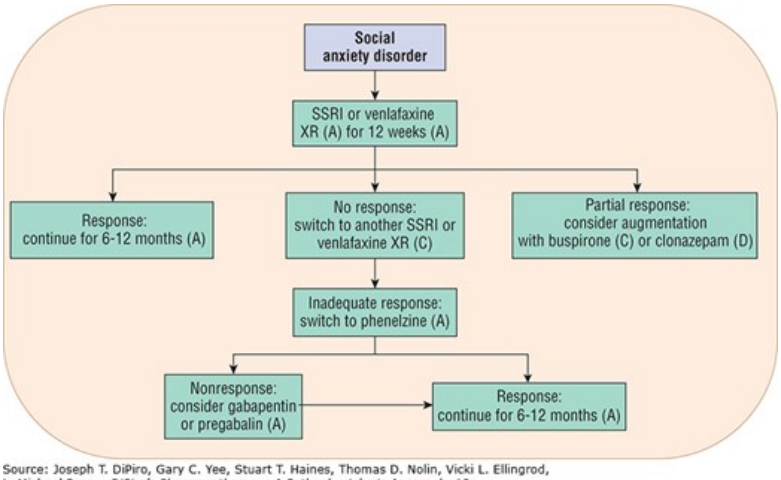


TABLE 90-9

Medications Used in the Treatment of Social Anxiety Disorder

Medication	Brand Name	Initial Dose	Usual Range (mg/day)	Comments
SSRIs				
Citalopram	Celexa	20 mg/day	20-40	Dosage used in clinical trials; maximum dose of 40 mg limited by QT prolongation; available generically
Escitalopram	Lexapro	5 mg/day	10-20	Dosage used in clinical trials; available generically
Fluvoxamine CR	Luvox CR	100 mg	100-300	FDA-approved; available generically
Paroxetine	Paxil	10 mg/day	10-60	FDA-approved; available generically
Paroxetine CR	Paxil CR	12.5 mg/day	12.5-37.5	FDA-approved; available generically
Sertraline	Zoloft	25-50 mg/day	50-200	FDA-approved; available generically
SNRI				
Venlafaxine XR	Effexor XR	75 mg/day	75-225	FDA-approved; available generically
Benzodiazepine				
Clonazepam	Klonopin	0.25 mg/day	1-4	Dosage used in clinical trials; used as augmenting agent; available generically
MAOI				
Phenelzine	Nardil	15 mg at bedtime	60-90	Dosage used in clinical trials; available generically
Alternative Agents				
Buspirone	BuSpar	10 mg twice per day	45-60	Dosage used in clinical trials; used as augmenting agent; available generically
Gabapentin	Neurontin	100 mg three times a day	900-3,600	Dosage used in clinical trials; dosage adjustment required in renal impairment; available generically
Pregabalin	Lyrica	100 mg three times a day	600	Dosage used in clinical trials; dosage adjustment required in renal impairment; available generically
Quetiapine	Seroquel	25 mg at bedtime	25-400	Dosage used in clinical trials; available generically

CR, controlled-release; MAOI, monoamine oxidase inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; XR,

extended-release.

Data from References 2, 3, 21, 29, and 55.

Selective Serotonin Reuptake Inhibitors

Efficacy

Large trials of escitalopram, fluvoxamine (immediate- and controlled-release), paroxetine, sertraline, and venlafaxine extended-release have shown efficacy and tolerability. Results of studies with fluoxetine have been inconsistent. The onset of effect with SSRIs is delayed 4 to 8 weeks, and maximum benefit is often not observed until 12 weeks or longer. Large relapse prevention trials with escitalopram, paroxetine, and sertraline demonstrated relapse rates of 4% to 14% with continued medication treatment, compared with 36% to 39% with placebo.[55,57]

Dosing and Administration

The SSRIs should be initiated at doses similar to those used for the treatment of depression and administered as a single daily dose (see Table 90-9). If the patient suffers from comorbid panic disorder, the SSRI dose should be started at one-fourth or one-half of the dose. The dose-response curve for SSRIs tends to be relatively flat, but individual patients can require higher doses. Increase the dose as tolerated in patients who have not responded after 4 weeks of therapy.[55-58] When discontinuing an SSRI, the dosage should be tapered monthly (ie, decreasing sertraline by 50 mg or paroxetine by 10 mg) to reduce the risk of relapse and discontinuation symptoms.

Venlafaxine

Efficacy

The efficacy of venlafaxine extended-release was established in four double-blind, parallel-group, 12-week, multicenter, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study.[31] Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these five trials, venlafaxine extended-release was significantly more effective than placebo on change from baseline to end point on the LSAS total score.[31]

Adverse Medication Reactions

Include anorexia, dry mouth, nausea, insomnia, and sexual dysfunction (see Table 90-6).

Dosing and Administration

Additional therapeutic benefits of venlafaxine extended-release above 75 mg/day have not been shown.[31] Venlafaxine should be tapered slowly (ie, decreasing by 37.5 mg/month) to decrease the risk of relapse during discontinuation.

Alternative Agents

Benzodiazepines

Benzodiazepines are commonly used in the treatment of patients who cannot tolerate or fail to respond to antidepressants. They are not considered first-line therapy for SAD because of concerns over the adverse medication reactions, potential for physical dependence, the possibility of rebound anxiety, and ineffectiveness in the treatment of depression. Clonazepam is the most extensively studied benzodiazepine for the treatment of generalized SAD.[55-58]

If clonazepam is prescribed, the acute phase of therapy is about 1 month. Patients should be instructed not to decrease or discontinue clonazepam without consulting their clinician because of the risks of rebound anxiety and withdrawal symptoms. Clonazepam should be gradually tapered at a rate not to exceed 0.25 mg every 2 weeks.

Antiseizure Medications

Gabapentin and pregabalin were effective in controlled trials, whereas levetiracetam was ineffective.[55-59]

β-Blockers

β-Blockers decrease the perception of anxiety by blunting the peripheral autonomic symptoms of arousal (eg, rapid heart rate, sweating, blushing, and tremor), and they are often used to decrease anxiety in performance-related situations.[55] For patients with performance anxiety, 10 to 80 mg of propranolol or 25 to 100 mg of atenolol can be taken 1 hour before a performance as needed. A test dose should be taken at home before the presentation to assure that β-blockade is sufficient and there are no adverse events. Controlled trials with β-blockers do not support daily use in SAD.[18]

Treatment Refractory Symptoms

9 An adequate antidepressant trial usually consists of 8 to 12 weeks (at maximum dosages).[55-58] Subsequent options include a trial of a second SSRI or venlafaxine extended-release. Some patients experience clinical benefit during the first 4 weeks of therapy.[55-58] If nonresponsiveness continues, a trial of an alternative agent is warranted.

There are little data on the choice of treatments if there is a partial response to antidepressant therapy in SAD. Published studies offer preliminary support for the combination of an SSRI with a benzodiazepine, gabapentin, or pregabalin.[55-58]

Second-generation antipsychotics and MAOIs are options in treatment-resistant SAD. Quetiapine monotherapy showed a large effect size on the Social Phobia Inventory when compared with placebo.[55-58] Although phenelzine is effective in 77% of patients with SAD,[2,18] dietary restrictions, potential interactions, and adverse medication reactions (eg, weight gain and hypertensive crisis) have limited its use. If a patient is switched from another antidepressant to phenelzine, an appropriate washout period should be followed. See Chapter 88 for more detail.

Special Populations

SAD can present in children of preschool to elementary school age. If the disorder is not treated, it can persist into adulthood and increase the risk of depression and SUD. Both CBT and social skills training are effective nonpharmacologic therapies in children.[55-58] Placebo-controlled and open-label trials have provided evidence of efficacy of pharmacotherapy with an SSRI or SNRI in children between ages 6 and 17 years.[2,18,55-58] Children and adolescents prescribed an SSRI or SNRI for social anxiety (or for other purposes) should be closely monitored for increased risk of suicidal ideation. Headache, nausea, drowsiness, insomnia, jitteriness, and stomachaches were reported in children receiving antidepressants.[55-58]

Benzodiazepines should be reserved as the last-line agents in children with SAD.[18,50] If prescribed, they should be used for the shortest time period possible. The adverse reactions of benzodiazepines in children include drowsiness, oppositional behavior, disinhibition, and fatigue.

Approximately one-fifth of patients with SAD also suffer from an alcohol use disorder, as many people with SAD report that they use alcohol to cope with anxiety. Paroxetine significantly reduced social anxiety and the frequency and severity of alcohol use in patients with SAD and an alcohol use disorder.[60] Neither MAOIs nor benzodiazepines are appropriate therapy for patients with SAD and alcohol use disorder as SSRIs are the medications of choice.

Evaluation of Therapeutic Outcomes

10 The pharmacotherapy of SAD can be monitored in three principal domains: SAD symptoms (eg, fears and physical symptoms), functionality, and well-being or overall improvement.[24,25,58] Response to pharmacotherapy in SAD is defined as a stable, clinically meaningful improvement, where patients no longer have the full range of symptoms but typically continue to experience more than minimal symptoms.[24,25,58]

During the acute phase of treatment, patients should be seen weekly while the medication dosage is titrated. Once the patient responds and the dosage is stabilized, the patient can be seen monthly. Many patients report improvement during the first 4 weeks of therapy, but more than one-

quarter of those who do not have a response at week 8 may have a response at 12 weeks. At each visit, the patient should be asked about adverse medication reactions and improvement in symptoms. The patient should be instructed to keep a diary to record fear levels, physical symptoms, cognitions, and anxious behaviors in actual exposures to social situations. The LSAS is a clinician-rated scale of clinical severity which can be used to assess change in SAD for monitoring response.[61] Patients can use the Social Phobia Inventory for self-assessment of SAD symptoms.[58,61] Full remission is defined as a complete resolution of symptoms across the three SAD domains that is maintained for 3 months or an LSAS score of less than or equal to 30 points.[55]

TREATMENT—SPECIFIC PHOBIA

Specific phobia is considered unresponsive to pharmacotherapy, although highly responsive to CBT. The use of benzodiazepines or paroxetine in patients who failed CBT is supported by limited data. Benzodiazepines can be detrimental in patients with specific phobias treated with CBT.[21]

CONCLUSION

Anxiety disorders are common in the population and occur concurrently with other psychiatric disorders. The proper management of anxiety disorders begins with the correct diagnosis as not all patients should receive antianxiety agents. Nonpharmacologic interventions often are effective alone or when combined with pharmacotherapy.

There are several subtypes of anxiety disorders, and the diagnosis determines the type of medication and nonpharmacologic intervention selected. Although benzodiazepines remain the medications of choice for situational anxiety, antidepressants have emerged as first-line therapy for GAD, panic disorder, and SAD. Benzodiazepines are reserved for use in situations requiring immediate anxiety relief during the first 2 to 4 weeks of therapy with a long-term agent such as an antidepressant. Antidepressants, including the SSRIs and SNRIs, and the benzodiazepines clonazepam and alprazolam are used extensively in patients with GAD, panic disorder, and SAD.

The long-term goal of therapy for GAD, panic disorder, and SAD is remission of core anxiety symptoms with no impairment in functionality, minimal anxiety, and no depressive symptoms. Augmentation with antiseizure medications and SGAs shows some promise in treatment-resistant cases.

ABBREVIATIONS

ACC	anterior cingulate cortex
CBT	cognitive behavioral therapy
CNS	central nervous system
CRF	corticotropin-releasing factor
DA	dopamine
DMDZ	desmethyldiazepam
GABA	γ-aminobutyric acid
GAD	generalized anxiety disorder
GI	gastrointestinal
HAM-A	Hamilton Anxiety Rating Scale
5-HT	serotonin

LC	locus ceruleus
LSAS	Liebowitz Social Anxiety Scale
NAMI	National Alliance for Mental Illness
MAOI	monoamine oxidase inhibitor
NE	norepinephrine
PAG	periaqueductal gray
PHQ-9	Patient Health Questionnaire-9
QOL	quality of life
SAD	social anxiety disorder
SERT	serotonin reuptake transporter
SGA	second-generation antipsychotic
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUD	substance use disorder
TCA	tricyclic antidepressant

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013:189–233.

2. 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. [PubMed: 25081580]

3. Bandelow B, Sher L, Bunevicius R et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract.* 2012;16:77–84. [PubMed: 22540422]

4. Roy-Byrne P. Treatment-refractory anxiety; definition, risk factors, and treatment challenges. *Dialogues Clin Neurosci.* 2015;17(2):191–206. [PubMed: 26246793]

5. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci.* 2015;17(3):327–335. [PubMed: 26487813]

6. DeMartini J, Patel G, Fancher TL. Generalized anxiety disorder. *Ann Intern Med.* 2019;170(7):ITC49–ITC64. 10.7326/AITC201904020 [PubMed: 30934083] .

7. Niles AN, Dour H, Stanton AL et al. Anxiety and depressive symptoms and medical illness among adults with anxiety disorders. *Psychosom Res.* 2015;78(2):109–115.

8. Craske MG, Stein MB, Elay TC et al. Anxiety disorders. *Nat Rev Dis Primers.* 2017;3:17024. doi: 10.1038/nrdp.2017.24.

9. Martin EI, Ressler KJ, Binder E, et al. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. *Psychiatr Clin North Am.* 2009;32:549–575. [PubMed: 19716990]

10. LeDoux JE, Pine DS. Using neuroscience to help understand fear and anxiety: a two-system framework. *Am J Psychiatry.* 2016;173(11):1083–1093. [PubMed: 27609244]

11. Bandelow B, Baldwin D, Abelli M, et al. Biological markers for anxiety disorders, OCD and PTSD: a consensus statement. Part I: neuroimaging and genetics. *World J Biol Psychiatry.* 2017;17(5):321–365.

12. Bandelow B, Baldwin D, Abelli M, et al. Biological markers for anxiety disorders, OCD and PTSD: a consensus statement. Part II: neurochemistry, neurophysiology and neurocognition. *World J Biol Psychiatry.* 2017;18(3):162–214. [PubMed: 27419272]

13. Nuss P. Anxiety disorders and GABA neurotransmission: a disturbance of modulation. *Neuropsychiatr Dis Treat.* 2015;11:165–175. [PubMed: 25653526]

14. Imai H, Tajika A, Chen P et al. Azapirones versus placebo for panic disorder in adults. *Cochrane Database Syst Rev.* 2014;(9):CD010828. doi: 0.1002/14651858.CD010828.pub2.

15. Warwick JM, Carey PD, Cassimjee N, et al. Dopamine transporter binding in social anxiety disorder: the effect of treatment with escitalopram. *Metab Brain Dis.* 2012;27(2):151–158. [PubMed: 22350963]

16. Maron E, Nutt D. Biological markers of generalized anxiety disorder. *Dialogues Clin Neurosci.* 2017;19:147–157. [PubMed: 28867939]

17. Reinhold JA, Rickel K. Pharmacological treatment for generalized anxiety disorder in adults: an update. *Expert Opin Pharmacother.* 2015;16(11):1669–1681. [PubMed: 26159446]

18. National Institute for Health and Care Excellence: Guidance. Social anxiety disorder: recognition, assessment and treatment. NICE Clinical Guideline 159. May 2013. Available at: http://www.nice.org.uk/guidance/cg159. Accessed November 11, 2021.

19. Abejuela HR, Osser DN. The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for generalized anxiety disorder. *Harv Rev Psychiatry.* 2016;24(4):243–256. [PubMed: 27384395]

20. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Panic Disorder*. Arlington, VA: American Psychiatric Association; 2009. http://www.psychiatryonline.com/pracGuide/pracGuideTopic_9.aspx. Accessed November 11, 2021. Accessed December 19, 2018.

21. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Pharmacology. *J Psychopharmacol.* 2014;28(5):403–439. [PubMed: 24713617]

22. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary, and community care. NICE Clinical Guideline 113. January 2011. Available at: http://www.nice.org.uk/guidance/cg113. Accessed November 11, 2021.

23. Stein MB, Sareen J. Generalized anxiety disorder. *N Engl J Med.* 2015;373:2059–2068. [PubMed: 26580998]

24. Bostwick JR, Cusher MI, Yasugi S. Benzodiazepines: a versatile clinical tool. *Current Psychiatry.* 2012;11(4):55–64.

25. PL Detail-Document, Benzodiazepine Toolbox. Pharmacist's Letter/Prescriber's Letter. August 2014.

26. Benzodiazepines. Facts and Comparisons® eAnswers (Online). Wolters Kluwer Health Inc., 2018. Available at: http://www.wolterskluwercdi.com/facts-comparisons-online/. Accessed November 11, 2021.

27. Hershenberg R, Gros DF, Brawman-Mintzer O. Role of atypical antipsychotics in the treatment of generalized anxiety disorder. *CNS Drugs.* 2014;28(6):519–533. [PubMed: 24794100]

28. Cymbalta [package insert]. Indianapolis, IN: Eli Lily and Company; December 2017.

29. Lexapro [package insert]. Madison NJ: Allergan Allergan; September 2021.

30. Paxil [package insert]. Weston, FL: Apotex Corporation; October 2021.

31. Effexor XR [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc, a subsidiary of Pfizer Inc.; July 2021.

32. Gommoll C, Forero G, Mathews M, et al. Vilazodone in patients with generalized anxiety disorder: a double-blind, randomized, placebo-controlled, flexible-dose study. *Int Clin Psychopharmacol.* 2015;30(6):297–306. [PubMed: 26291335]

33. Pae CU, Wang SM, Han C et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. *J Psychiatr Res.* 2015;64:88–98. [PubMed: 25851751]

34. Vistaril [package insert]. New York, NY: Pfizer Labs; June 2020.

35. The International Psychopharmacology Algorithm Project. IPAP—Generalized Anxiety Disorder Algorithm. Available at: http://www.ipap.org/gad/index.php. Accessed November 11, 2021.

36. Kong W, Deng H, Wan J, et al. Comparative remission rates and tolerability of drugs for generalised anxiety disorder: a systematic review and network meta-analysis of double-blind randomized controlled trials. *Front Pharmacol.* 2020;11:580858–580858. 10.3389/fphar.2020.580858 [PubMed: 33343351] .

37. David DJ, Samuels BA, Rainer Q et al. Neurogenesis-dependent and independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron.* 2009;62(4):479–493. [PubMed: 19477151]

38. Klonopin [package insert]. San Francisco, CA: Genentech Inc; February 2021.

39. Xanax XR [package insert]. New York, NY: Pharmacia and Upjohn Company Inc; March 2021.

40. Chen X, van Gerven J, Cohen A, Jacobs G Human pharmacology of positive GABA-A subtype-selective receptor modulators for the treatment of anxiety. *Acta Pharmacol Sin.* 2019;40(5):571–582. 10.1038/s41401-018-0185-5 [PubMed: 30518829] .

41. Labbate LA, Fava M, Rosenbaum JF, Arana GW. *Handbook of Psychiatric Therapy.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:163–192.

42. Lader M. Benzodiazepine harm: how can it be reduced? *Br J Clin Pharmacol.* 2014;77(2):295–301. [PubMed: 22882333]

43. Gold J, Ward K. Pharmacist Toolkit: Benzodiazepine Taper. College of Psychiatric and Neurologic Pharmacists 2018. Available at: https://cpnp.org/guideline/benzo. Accessed November 11, 2021.

44. Caniff K, Telega E, Bostwick JR, Gardner KN. Pregabalin as adjunctive therapy in benzodiazepine discontinuation. *Am J Health Syst Pharm.*

2018;75(2):67–71. 10.2146/ajhp160712
[PubMed: 29317396] .

45. Canadian Agency for Drugs and Technologies in Health. Discontinuation strategies for patients with long-term benzodiazepine use: A review of clinical evidence and guidelines. Ottawa (ON); July 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0078914/pdf/PubMedHealth_PMH0078914.pdf. Accessed November 11, 2021.

46. Generoso MB, Trevizol AP, Kasper S, et al. Pregabalin for generalized anxiety disorder: an updated systematic review and meta-analysis. *Int Clin Psychopharmacol.* 2017;32:49–55. [PubMed: 27643884]

47. Sarris J, et al. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. *Phytother Res.* 2018;32(7):1147–1162. 10.1002/ptr.6055
[PubMed: 29575228] .

48. McAllister-Williams RH, Baldwin DS, Cantwell R, et al. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. *J Psychopharmacol.* 2017;31(5):519–552. 10.1177/0269881117699361
[PubMed: 28440103] .

49. Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. *Gen Hosp Psychiatry.* 2013;35:3–8. [PubMed: 23044244]

50. Wehry AW, Beesdo-Baum K, Hennelly MM et al. Assessment and treatment of anxiety disorders in children and adolescents. *Curr Psychiatry Rep.* 2015;17(7):52. doi: 10.1007/s11920-015-0591-z.

51. Andreescu C, Varon D. New research on anxiety disorders in the elderly and an update on evidence-based treatments. *Curr Psychiatry Rep.* 2015;17(7):53. doi: 10.1007/s11920-015-0595-8.

52. Karaiskos D, Pappa D, Tzavellas E, et al. Pregabalin augmentation of antidepressants in older patients with comorbid depression and generalized anxiety disorder: an open-label study. *Int J Geriatr Psychiatry.* 2013;28(1):100–105. [PubMed: 22431439]

53. Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. *Int Clin Psychopharmacol.* 2012;28:33–45.

54. Du Y, Du B, Diao Y, et al. Comparative efficacy and acceptability of antidepressants and benzodiazepines for the treatment of panic disorder: a systematic review and network meta-analysis. *Asian J Psychiatr.* 2021;60:102664–102664. 10.1016/j.ajp.2021.102664
[PubMed: 33965693] .

55. Blanco C, Bragdon LB, Schneier FR et al. The evidence-based pharmacotherapy of social anxiety disorder. *Int J Neuropsychopharmacol.* 2013;16(1):235–249. [PubMed: 22436306]

56. Leichsenring F, Leweke F. Social anxiety disorder. *N Engl J Med.* 2017;376:2255–2264. [PubMed: 28591542]

57. Pelissolo A, Abou Kassm S, Delhay L. Therapeutic strategies for social anxiety disorder: where are we now? *Expert Rev Neurother.* 2019;19(12):1179–1189. 10.1080/14737175.2019.1666713
[PubMed: 31502896] .

58. Dalrymple KL. Issues and controversies surrounding the diagnosis and treatment of social anxiety disorder. *Expert Rev Neurother.* 2012;2(8):993–1008.

59. Kawalec P, Cierniak A, Pilc A et al. Pregabalin for the treatment of social anxiety disorder. *Expert Opin Investig Drugs.* 2015;24(4):585–594.
[PubMed: 25361817]

60. Ipser JC, Wilson D, Akindipe TO et al. Pharmacotherapy for anxiety and comorbid alcohol use disorders. *Cochrane Database Syst Rev.* 2015;1:CD007505.

61. Osório Fde L, Crippa JA, Loureiro SR. Instruments for the assessment of social anxiety disorder: validation studies. *World J Psychiatry.* 2012;2(5):83–5. 10.5498/wjp.v2.i5.83
[PubMed: 24175172] .

SELF-ASSESSMENT QUESTIONS

1. A 30-year-old patient presents to the clinic complaining of feeling anxious. The patient endorses feeling on edge and their mind going blank which are interfering with their job as a salesperson. These symptoms have been occurring nearly every day for the past 7 months and are difficult to control. The presence of which of the following symptoms would indicate that the patient meets the *Diagnostic and Statistical Manual* Version 5 criteria for generalized anxiety disorder?

   A. Suicidal ideation, guilt, weight loss

   B. Fear of dying, paresthesias, chest pain

   C. Fatigue, muscle tension, sleep disturbance

   D. Fear of being humiliated, blushing, sweating

2. Which of the following neurotransmitters is a major inhibitory neurotransmitter in the central nervous system and is involved in the pathophysiology of anxiety?

   A. Dopamine

   B. Norepinephrine

   C. Gamma-aminobutyric acid

   D. Corticotropin-releasing factor

3. A 62-year-old patient with diabetes, depression, hyperlipidemia, and peptic ulcer disease presents with symptoms of anxiety including trembling, irritability, and palpitations. The patient's medication regimen includes metformin, bupropion, rosuvastatin, and famotidine. Which medication is most likely to contribute to symptoms of anxiety?

   A. Metformin

   B. Bupropion

   C. Rosuvastatin

   D. Famotidine

4. A 27-year-old patient is newly diagnosed with generalized anxiety disorder in the outpatient clinic. The treatment team would like to prescribe escitalopram. What daily starting dose would you recommend?

   A. 10 mg

   B. 12.5 mg

   C. 20 mg

D. 50 mg

5. A 55-year-old patient with a 25-year history of generalized anxiety disorder, a 10-year history of alcohol use disorder, and hepatic impairment presents to the outpatient clinic complaining of significant anxiety related to recent break up of a relationship and loss of their job. The patient is currently on no medication. Which of the following anxiolytics would be the safest to prescribe?

   A. Duloxetine 30 mg PO once daily

   B. Clonazepam 0.5 mg PO twice a day

   C. Alprazolam 0.5 mg PO three times a day

   D. Hydroxyzine 25 mg PO four times a day

6. A 22-year-old college student with social anxiety disorder has been treated with sertraline 100 mg daily. The student has responded well to the sertraline in the acute phase of treatment and asks how long the sertraline should be continued. The sertraline should be continued for at least how many months?

   A. 1 month

   B. 3 months

   C. 6 months

   D. 12 months

7. Which of the following medications interact with alprazolam to reduce alprazolam concentrations?

   A. Ritonavir

   B. Mirtazapine

   C. Fluvoxamine

   D. St. John's Wort

8. A patient with social anxiety disorder has been treated successfully with venlafaxine extended-release 150 mg daily for 6 months. The patient inquires about discontinuation of therapy. Which of the following is the most appropriate plan for discontinuation of venlafaxine extended-release?

   A. Continue therapy for 6 more months, then attempt to taper the venlafaxine over 4 to 6 months

   B. Add lorazepam to the regimen and attempt to taper venlafaxine extended-release over 2 months

   C. Continue therapy for 3 more months, then attempt to taper venlafaxine extended-release by decreasing the dose 25% weekly

   D. Convert venlafaxine to fluoxetine, then discontinue fluoxetine after 6 months of therapy

9. A patient has been treated with alprazolam 1 mg three times daily for panic disorder for 12 months. Upon discontinuation of therapy, the alprazolam should be tapered over how many weeks to minimize withdrawal and reduce the chance for relapse?

   A. 2 weeks

   B. 4 weeks

   C. 6 weeks

D. 12 weeks

10. A patient with panic disorder has failed therapy with fluoxetine and escitalopram. Based on evidence-based treatment guidelines, which of the following medications would be preferred for the next trial of pharmacotherapy?

    A. Bupropion

    B. Pregabalin

    C. Mirtazapine

    D. Venlafaxine

11. A 45-year-old patient with generalized anxiety disorder has been on paroxetine 20 mg daily for 2 weeks and returns today for a follow-up appointment. In addition to asking the patient questions to determine efficacy, emergence of adverse effects, and adherence, which of the following items would provide an objective measure of the antianxiety efficacy?

    A. Sheehan Disability Scale (SDS)

    B. Brief Panic Disorder Screen (BPDS)

    C. Patient Health Questionnaire-9 (PHQ-9)

    D. Hamilton Anxiety Rating Scale (HAMD)

12. A 26-year-old student nurse is diagnosed with panic disorder and is prescribed fluoxetine. Which of the following is a key component of patient education that should be provided to the student?

    A. Minimize intake of nicotine and caffeine

    B. Antidepressant medication should be taken at nighttime

    C. Breathing into a paper bag is a helpful coping mechanism when having a panic attack

    D. Cognitive behavioral therapy is unlikely to be beneficial while prescribed medication

13. You are discussing goals and objectives of pharmacotherapy of anxiety disorders with your learning team. Which of the following is the long-term goal of therapy in the treatment of each of the anxiety disorders?

    A. Few to minimal core symptoms

    B. Partial response after 12 weeks

    C. Ability to taper adjunctive agent

    D. Complete remission of symptoms

14. A 45-year-old patient presents with generalized anxiety disorder. The patient is not interested in pharmacotherapy but is agreeable to nonpharmacologic methods of treatment. If nonpharmacologic methods are recommended, which of the following types of psychotherapy would be most appropriate?

    A. Psychological debriefing

    B. Cognitive behavioral therapy

    C. Dialectical behavioral therapy

D. Eye movement desensitization and reprocessing

15. A 42-year-old factory worker is starting pharmacotherapy for generalized anxiety disorder. The patient is very concerned about any sedation or cognitive impairment from medications that might interfere with employment. Which of the following medications should be avoided in this patient case?

    A. Diazepam

    B. Fluoxetine

    C. Duloxetine

    D. Buspirone

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Fatigue, muscle tension, and sleep disturbance are symptoms of generalized anxiety disorder. Suicidal ideation, guilt, and weight loss are symptoms of depression. Fear of dying, paresthesias, and chest pain are consistent with panic disorder. Fear of being humiliated, blushing, sweating are symptoms of social anxiety disorder. See the sections on "Clinical Presentation" for details on each anxiety disorder.

2. **D.** Gamma-aminobutyric acid is the major inhibitory neurotransmitter in the central nervous system. Norepinephrine is involved in implanting the fear response, while the roles of dopamine and serotonin in anxiety are not as well defined. Corticotropin-releasing factor is a peptide hormone that is released in response to stress. See the "Pathophysiology" section.

3. **A.** The starting dose of escitalopram for generalized anxiety disorder is 10 mg daily. The other doses are too high for an initial dose. See Table 90-5.

4. **D.** Hydroxyzine is the best choice because it is an antihistamine and lacks the risk of a substance use disorder in this patient with a history of alcohol use disorder. Clonazepam and alprazolam should be avoided because this patient is at risk of misusing these benzodiazepines. Duloxetine should not be used in patients with hepatic impairment because of reports of hepatitis and elevated hepatic enzymes; rare cases of hepatic failure have been reported. See the section on "Alternative Medication Treatments" for generalized anxiety disorder.

5. **B.** Bupropion is the most likely medication to cause anxiety of those that the patient is taking. Metformin, rosuvastatin, and famotidine are not associated with anxiety. See Table 90-2.

6. **D.** Long-term use of benzodiazepines (ie, 1 year or longer) requires a 2- to 4-month slow taper. Since this patient has been treated for 12 months, a taper of 12 weeks (3 months) would be most appropriate. See section on "Benzodiazepine Discontinuation."

7. **D.** St. John's Wort is a CYP3A4 inducer that can reduce alprazolam plasma concentration and concurrent use should be avoided. Ritonavir and fluvoxamine are both CYP3A4 inhibitors and concurrent use with alprazolam would be expected to increase alprazolam plasma concentrations. There is not a pharmacokinetic interaction between mirtazapine and alprazolam, but combined use can result in increased central nervous system depression. See the section on "Generalized Anxiety Disorder" for details of Pharmacokinetics of Benzodiazepine.

8. **A.** Since the patient has been taking the venlafaxine extended-release for 6 months with good response, and the minimum duration of treatment is 12 months, the medication should be continued for 6 more months and then tapered over 4 to 6 months to avoid discontinuation syndrome and recurrence of symptoms. There is no need to add a benzodiazepine or change the venlafaxine to fluoxetine. See section on "Maintenance Phase and Discontinuation" under panic disorder.

9. **D.** Generalized anxiety disorder, social anxiety disorder, and panic disorder should all be treated for a minimum of 12 months after resolution of symptoms to avoid relapse and recurrence of symptoms. See the sections on "Maintenance Phase and Discontinuation" for each disorder.

10. **D.** When a patient has failed one or two trials with a selective serotonin reuptake inhibitor, treatment with venlafaxine, a serotonin norepinephrine reuptake inhibitor, is most appropriate. Bupropion has the potential to make anxiety worse, pregabalin has not been studied in panic disorder, and mirtazapine is not a first-line treatment option. See Fig. 90-2 and "Serotonin–Norepinephrine Reuptake Inhibitors" section under panic disorder.

11. **D.** The Hamilton Anxiety Rating Scale is the best scale for measuring the efficacy of medication for generalized anxiety disorder and it is a clinician-rated scale. The Sheehan Disability Scale is a self-rated scale that assesses the impact of a disorder on a patient's life; it is not sensitive for medication effects. The Brief Panic Disorder Screen is used to screen patients for panic disorder. The Patient Health Questionnaire 9 is used for assessing and monitoring depression severity. See the section on "Evaluation of Therapeutic Outcomes" for generalized anxiety disorder.

12. **A.** A key component of education provided to patients with anxiety disorders is to minimize intake of nicotine and caffeine. Both of these medications are stimulants that can increase symptoms of anxiety, especially in panic disorder. Fluoxetine should be taken in the morning because it is activating. Breathing into a paper bag during a panic attack has been shown to make symptoms worse and therefore other breathing exercises are more appropriate. Cognitive behavioral therapy is a very helpful psychological treatment for panic disorder in conjunction with medication therapy. See "Nonpharmacologic Therapy" under panic disorder.

13. **D.** The long-term goal of generalized anxiety disorder, panic disorder, and social anxiety disorder is complete remission of symptoms. While having few to minimal core symptoms, response to medication, and decreased need for adjunctive agents are desirable, the long-term goal should always be complete remission of the disorder. See the section "Key Concepts" number two.

14. **B.** Cognitive behavioral therapy is the psychological therapy recommended for generalized anxiety disorder. Psychological debriefing and eye movement desensitization and reprocessing are used to treat anxiety related to trauma. Dialectical behavioral therapy is used primarily with personality disorders. See the section on "Nonpharmacologic Therapy" for generalized anxiety disorder.

15. **A.** In comparing class of medications for anxiety disorders, they have distinctive adverse effects. In this case, the patient needs to avoid medications that may cause sedation and cognitive impairment. Therefore, diazepam (benzodiazepine) would not be appropriate treatment for generalized anxiety. Fluoxetine, duloxetine or buspirone would be appropriate treatment choices. See sections on "Benzodiazepines Therapy" and "Antidepressant Therapy" under generalized anxiety disorder.