Chapter 66: Anxiety Disorders

INTRODUCTION

- A*nxiety disorders* (eg, generalized anxiety disorder [GAD] and panic disorder [PD]) have prominent features of anxiety and avoidance that are irrational or that impair functioning. In posttraumatic stress disorder (PTSD), there is previous exposure to trauma and intrusive, avoidant, and hyperarousal symptoms.

ETIOLOGY

- Evaluation of anxiety requires a physical and mental status examination; complete psychiatric diagnostic exam; appropriate laboratory tests.
- Anxiety symptoms may be associated with medical illnesses (**Table 66-1**) or medications (**Table 66-2**), and they may be present in several major psychiatric illnesses (eg, mood disorders, schizophrenia, organic mental syndromes, and substance withdrawal).

TABLE 66-1

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 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

TABLE 66-2

Drugs Associated with Anxiety Symptoms

Anticonvulsants: 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: ma huang, ginseng, ephedra
Illicit substances: ecstasy, marijuana
Nonsteroidal anti-inflammatory drugs: ibuprofen, indomethacin
Stimulants: amphetamines, caffeine, cocaine, methylphenidate, nicotine
Sympathomimetics: pseudoephedrine, phenylephrine
Thyroid hormones: levothyroxine
Toxicity: anticholinergics, antihistamines, digoxin

PATHOPHYSIOLOGY

- *Noradrenergic model.* The autonomic nervous system of anxious patients is hypersensitive and overreacts to various stimuli. The locus ceruleus (LC) may have a role in regulating anxiety, because it activates norepinephrine release and stimulates the sympathetic and parasympathetic nervous systems. Chronic noradrenergic overactivity downregulates α_2-adrenoreceptors in patients with GAD and PTSD, while this receptor is hypersensitive in PD. Drugs with anxiolytic or antipanic effects (eg, benzodiazepines and antidepressants) inhibit LC firing, decrease noradrenergic activity, and block the effects of anxiogenic drugs.

- γ-*Aminobutyric acid (GABA) receptor model.* GABA is the major inhibitory neurotransmitter in the central nervous system (CNS). Benzodiazepines enhance the inhibitory effects of GABA, which regulates or inhibits serotonin (5-hydroxytryptamine; 5-HT), norepinephrine, and dopamine activity. The number of $GABA_A$ receptors can change with alterations in the environment, and GABA receptor subunit expression can be altered by hormonal changes. Abnormal functioning of several neurotransmitter systems, including norepinephrine, GABA, glutamate, dopamine, and 5-HT, may affect manifestations of anxiety disorders.

- *5-HT model.* Abnormalities in serotonergic functioning may play a role. Preclinical models suggest that greater 5-HT function facilitates avoidance behavior; but primate studies show that reducing 5-HT increases aggression. GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways. The selective serotonin reuptake inhibitors (**SSRIs**) increase 5-HT levels at the synapse and are effective in blocking manifestations of panic and anxiety.

- Cortisol reduces the stress response by tempering the sympathetic reaction. Patients with PTSD hypersecrete corticotropin-releasing factor but have subnormal levels of cortisol at the time of trauma and chronically. Dysregulation of the hypothalamic–pituitary–adrenal axis may be a risk factor for eventual development of PTSD.

- Neuroimaging studies support the role of the amygdala, anterior cingulate cortex, and insula in the pathophysiology of anxiety. In GAD, there is an abnormal increase in the brain's fear circuitry and increased activity in the prefrontal cortex. Patients with PD have abnormalities of midbrain structures. In PTSD, the amygdala plays a role in the persistence of traumatic memory. Hypofunctioning in the ventromedial prefrontal cortex is theorized to prevent extinction in patients with PTSD and is inversely correlated with severity of symptoms.

- Glutamate signaling abnormalities may distort amygdala-dependent emotional processing under stress, which may contribute to the dissociative

and hypervigilant symptoms in PTSD.

GENERALIZED ANXIETY DISORDER: CLINICAL PRESENTATION AND DIAGNOSIS

- Psychological and cognitive symptoms of GAD include excessive anxiety, worries that are difficult to control, feeling keyed up or on edge, and trouble concentrating or mind going blank.
- Physical symptoms include restlessness, fatigue, muscle tension, sleep disturbance, and irritability.
- The diagnosis of GAD requires excessive anxiety and worry most days for at least 6 months with at least three physical symptoms present. Significant distress or impairment in functioning is present, and the disturbance is not caused by a substance or another medical condition.
- Women are twice as likely as men to have GAD. The illness has a gradual onset at an average age of 21 years. The course is chronic, with multiple exacerbations and remissions.

TREATMENT

- Goals of Treatment: The goals are to reduce severity, duration, and frequency of symptoms and improve functioning. The long-term goal is minimal or no anxiety symptoms, no functional impairment, prevention of recurrence, and improved quality of life.

Nonpharmacologic Therapy

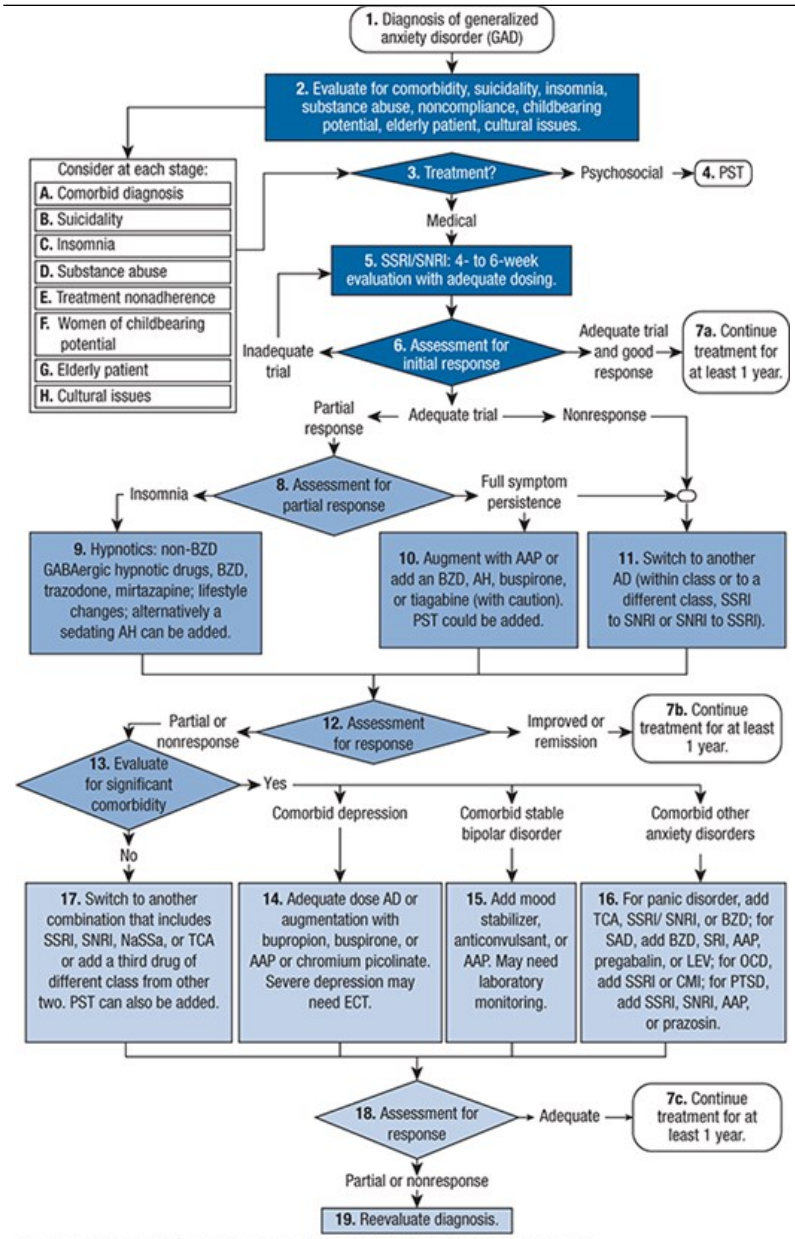
- Nonpharmacologic modalities include psychotherapy, short-term counseling, stress management, psychoeducation, meditation, and exercise. Ideally, patients with GAD should have psychological therapy, alone or in combination with antianxiety drugs. Cognitive behavioral therapy (CBT), though not widely available, is the most effective psychological therapy. Patients should avoid caffeine, nicotine, stimulants, excessive alcohol, and diet pills.
- A treatment algorithm from the International Psychopharmacology Algorithm Project (IMAP) is shown in **Figure 66-1**.

FIGURE 66-1

International Psychopharmacology Algorithm Project (IPAP) generalized anxiety disorder (GAD) algorithm flowchart.

Dark blue, first-line treatment (nodes 2, 3, 5, 6); medium blue, second-line treatment (nodes 8–12); light blue, third-line treatment, no comorbidity (nodes 13, 17, 18, 19); gray, third-line treatment, with comorbidity (nodes 14–16). 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 drug 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. (Used by permission of the International Psychopharmacology Algorithm Project. IPAP—Generalized Anxiety Disorder Algorithm. http://www.ipap.org./gad/index.php, accessed December 22, 2015.)

(AAP, atypical antipsychotic; 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; SNRI, serotonin-norepinephrine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Pharmacologic Therapy

- Drug choices for GAD and PD are shown in **Table 66-3**, and non-benzodiazepine antianxiety agents for GAD and their dosing are shown in **Table 66-4**.

TABLE 66-3

Drug Choices for Anxiety Disorders

Anxiety Disorder	First-Line Drugs	Second-Line Drugs	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

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

TABLE 66-4

Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder

Drug	Brand Name	Initial Dose	Usual Range (mg/day)[a]	Comments
Antidepressants				
Duloxetine	Cymbalta	30 or 60 mg/day	60–120	FDA-approved
Escitalopram	Lexapro	10 mg/day	10–20	FDA-approved, available generically
Imipramine	Tofranil	50 mg/day	75–200	Available generically
Paroxetine	Paxil Pexeva	20 mg/day	20–50	FDA-approved, available generically, avoid in pregnancy
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	Brintellix	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 (adult)	200–400	FDA-approved, available generically, also approved for children with anxiety and tension
Anticonvulsant				
Pregabalin	Lyrica	50 mg three times daily	150–600	Dosage adjustment required in renal impairment
Atypical antipsychotic				
Quetiapine XR	Seroquel XR	50 mg at bedtime	150–300	

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

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

XR, extended-release.

Antidepressants

- Antidepressants are effective for acute and long-term management of GAD (Table 66-4). They are the treatment of choice for long-term management of chronic anxiety, especially in the presence of depressive symptoms. **Venlafaxine extended-release**, **duloxetine**, **paroxetine**, and **escitalopram** are FDA-approved for GAD, and **imipramine** is considered a second-line agent. Antianxiety response requires 2–4 weeks or longer. See Chapter 68 for additional information on antidepressants.
- Selective serotonin reuptake inhibitors (SSRIs), extended-release venlafaxine, and duloxetine are effective in acute therapy (response rates of 60%–68%). In a meta-analysis, **fluoxetine** was most likely to achieve remission of GAD symptoms; sertraline was best tolerated.
- Common side effects and monitoring parameters for patients taking medications used for anxiety disorders are shown in **Table 66-5**.
- Some patients require small initial doses of antidepressants for the first week to limit the development of transient increased anxiety, also known as jitteriness syndrome.

- All antidepressants carry a black box warning regarding suicidality (suicidal thinking and behaviors) in children, adolescents, and young adults less than 25 years and recommends specific monitoring parameters (consult the FDA-approved labeling or the FDA website).
- Clinical practice guidelines recommend use of fluoxetine, sertraline, or citalopram for pregnant women; however, jitteriness, myoclonus, and irritability in the neonate and premature infant have been reported and paroxetine should be avoided due to cardiovascular malformation risk.

TABLE 66-5

Monitoring of Adverse Effects Associated with Medications Used for Anxiety Disorders

Medication Class/Drug	Adverse Drug 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 patients >65 years
	Thrombocytopenia	Complete blood count	
	Teratogenicity	Pregnancy test at baseline	Reported with citalopram
	QT prolongation	ECG	Avoid paroxetine in pregnancy; Pregnancy Category D
	Discontinuation syndrome	Patient interview	Before starting citalopram, consider ECG and measurement of QT interval in patients with cardiac disease
			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	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Suicidality	Patient interview	Contraindicated with narrow-angle glaucoma, prostatic hypertrophy, and urinary retention
	Anticholinergic effects	Patient interview	Significant reason for nonadherence
	Weight gain	Body weight, BMI, waist circumference	Administer dosage at bedtime when feasible
	Sexual dysfunction	Patient interview	At baseline and periodically in children and patients >40 years of age
	Sedation	Patient interview	Avoid abrupt discontinuation; taper doses
	Arrhythmia	ECG	
	Orthostatic hypotension	Blood pressure with position changes	
	Cholinergic rebound		

		Patient interview	
Benzodiazepines	Drowsiness, fatigue Anterograde amnesia and memory impairment Dependence Withdrawal symptoms Respiratory depression Psychomotor impairment Paradoxical disinhibition	Patient interview Patient interview Patient interview; Prescription Monitoring Program Physical examination; patient interview Respiratory rate Physical examination Physical examination; family report	Avoid operating large machinery; tolerance to sedation develops after repeated dosing Risk of anterograde amnesia is worsened with concomitant intake of alcohol Monitor for early refills or escalation of dosage Taper doses on discontinuation Avoid administering with other CNS depressants (ie, opioids, alcohol) Increased risk of falls Increase in anxiety, irritability, or agitation may be seen in older patients or children
Other drugs			
Buspirone Phenelzine Pregabalin Quetiapine	Nausea, abdominal pain Drowsiness, dizziness Jitteriness syndrome Suicidality Hypertensive crisis Orthostatic hypotension Dizziness, somnolence Peripheral edema Thrombocytopenia Weight gain Sedation Metabolic syndrome Akathisia Tardive dyskinesia Orthostatic hypotension	Patient interview Patient interview Patient interview Patient interview Blood pressure Blood pressure with position changes Patient interview Physical examination Complete blood count Body weight Patient interview Body weight, BMI, waist circumference, fasting lipids and glucose Patient interview Abnormal Involuntary Movement Scale Blood pressure with position changes	Typically transient Typically transient Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25 Tyramine-free diet and avoidance of drug interactions required Fasting labs at baseline and then periodically Fasting labs at baseline and then periodically

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

Benzodiazepines

- All benzodiazepines possess anxiolytic properties, although only 7 marketed agents have FDA approval for the treatment of GAD, as the other agents have different FDA-approved indications.
- Benzodiazepines are the most effective and frequently prescribed drugs for the treatment of acute anxiety (**Table 66-6**). About 65%–75% of patients with GAD have a marked to moderate response, and most of the improvement occurs in the first 2 weeks of therapy. They are more effective for somatic and autonomic symptoms of GAD, whereas antidepressants are more effective for the psychic symptoms (eg, apprehension and worry).

- The dose must be individualized. older patients are more sensitive to benzodiazepines and may experience falls when taking them.
- The most common side effect of benzodiazepines is CNS depression. Tolerance usually develops to this effect. Other side effects are disorientation, psychomotor impairment, confusion, aggression, excitement, ataxia, and anterograde amnesia (see Table 66-5).
- Start with low doses, and adjust weekly (see Table 66-6). 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
- Treatment of acute anxiety generally should be 2–4 weeks. Manage persistent symptoms with antidepressants.
- Long half-life benzodiazepines may be dosed once daily at bedtime, providing nighttime hypnotic and next day anxiolytic effects.
- Use low doses of short-elimination half-life agents in older patients.
- **Diazepam** and **clorazepate** have high lipophilicity and are rapidly absorbed and distributed into the CNS. They have rapid antianxiety effects, but a shorter duration of effect after a single dose than would be predicted based on half-life, as they are rapidly distributed to the periphery.
- **Lorazepam** and **oxazepam** are less lipophilic, have a slower onset, but a longer duration of action. They are not recommended for immediate relief of anxiety.
- **Avoid intramuscular (IM) diazepam** and **IM chlordiazepoxide** because of variability in rate and extent of absorption. **IM lorazepam** provides rapid and complete absorption.
- Several benzodiazepines are converted to desmethyldiazepam, which has a long half-life and can accumulate. Intermediate- or short-acting benzodiazepines are preferred for chronic use in older patients and those with liver disorders because of minimal accumulation and achievement of steady state within 1–3 days.
- Combining benzodiazepines with alcohol or other CNS depressants may be fatal.
- Addition of nefazodone, ritonavir, or ketoconazole (CYP3A4 inhibitors) can increase the blood levels of alprazolam and diazepam. Drugs that induce cytochrome CYP3A4 (eg, carbamazepine, St. John's wort) can reduce benzodiazepine levels. Drugs that inhibit or induce CYP2C19 (eg, fluoxetine, fluvoxamine, omeprazole) or *N*-acetyltransferase 2 activity can alter diazepam and clonazepam metabolism, respectively.
- Consult the drug interaction literature for more information on benzodiazepine drug interactions.
- Benzodiazepine use in pregnant women has been associated with teratogenic effects (ie, cleft lip and palate, "floppy baby syndrome," and neonatal withdrawal. Antidepressants are preferred. If a benzodiazepine must be used, diazepam and chlordiazepoxide may be preferred but may cause sedation, lethargy, and weight loss in breastfed infants.

TABLE 66-6

Benzodiazepine Antianxiety Agents

Drug	Brand Name	Approved Dosage Range (mg/day)	Maximum Dosage for older Patients (mg/day)	Approximate Equivalent Dose (mg)	Comments
Alprazolam[a]	Niravam[b], Xanax	0.75–4	2	0.5	Associated with interdose rebound anxiety
	Xanax XR	1–10[c]			
Chlordiazepoxide[a]	Librium	25–400	40	10	
Clonazepam[a]	Klonopin	1–4[c]	3	0.25–0.5	
	Klonopin Wafer[b]				
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 elderly
Oxazepam[a]	Serax	30–120	60	30	Preferred in elderly

[a]Available generically.

[b]Orally disintegrating formulation.

[c]Panic disorder dose.

XR, extended-release.

Benzodiazepine Discontinuation

- After benzodiazepines are abruptly discontinued, three events can occur: (1) rebound symptoms are an immediate but transient return of original symptoms with an increased intensity compared with baseline; (2) recurrence or relapse is the return of original symptoms at the same intensity as before treatment; or (3) withdrawal is the emergence of new symptoms and a worsening of preexisting symptoms.
- The onset of withdrawal symptoms is within 24–48 hours after discontinuation of short-elimination half-life benzodiazepines and 3–8 days after discontinuation of long-elimination half-life drugs.
- Discontinuation strategies include:

  ✔ A 25% per week reduction in dosage until 50% of the dose is reached, and then reduce by one eighth every 4–7 days. If therapy duration exceeds 8 weeks, a taper over 2–3 weeks is recommended, but if duration of treatment is 6 months, a taper over 4–8 weeks is reasonable. Longer durations of treatment may require a 2- to 4-month taper.

- Adjunctive use of **pregabalin** can help to reduce withdrawal symptoms during the benzodiazepine taper.

Abuse, Dependence, Withdrawal, and Tolerance

- Benzodiazepine dependence is defined by appearance of a withdrawal syndrome (ie, anxiety, insomnia, agitation, muscle tension, irritability, nausea, diaphoresis, nightmares, depression, hyperreflexia, tinnitus, delusions, hallucinations, and seizures) upon abrupt discontinuation.

  Those with a history of drug abuse should not receive benzodiazepines. Those with GAD and PD are at high risk for dependence because of the chronicity of the illnesses.

Buspirone

- **Buspirone** is a 5-HT_{1A} partial agonist that lacks anticonvulsant, muscle relaxant, sedative-hypnotic, motor impairment, and dependence-producing properties.
- It is a second-line agent for GAD because of inconsistent reports of long-term efficacy, and delayed onset of effect. It is an option for patients who fail other anxiolytic therapies or patients with a history of alcohol or substance abuse. It does not provide rapid or "as needed" antianxiety effects.
- Buspirone can be titrated in increments of 5 mg/day every 2 or 3 days as needed.
- The onset of anxiolytic effects requires 2 weeks or more; maximum benefit may require 4–6 weeks. Improvement in psychic symptoms precedes improvement in somatic symptoms.
- It may be less effective in patients who have previously taken benzodiazepines.
- It has a mean $t_{1/2}$ of 2.5 hours, and it is dosed two to three times daily (see Table 66-4).
- Buspirone may elevate blood pressure in patients taking a monoamine oxidase inhibitor (MAOI).
- Verapamil, itraconazole, and fluvoxamine can increase buspirone levels through CYP3A4 inhibition, and rifampin reduces buspirone blood levels 10-fold.

Alternative Pharmacotherapy

- **Hydroxyzine**, often used in primary care, is considered a second-line agent.
- **Pregabalin** produced anxiolytic effects similar to lorazepam, alprazolam, and venlafaxine in acute trials. Sedation and dizziness were the most common adverse effects.
- **Quetiapine** extended release, 150 mg/day, was superior to placebo and as effective as **paroxetine** 20 mg/day and **escitalopram** 10 mg/day, but with earlier onset of action. Quetiapine is not FDA-approved for GAD and the long-term risks are unknown.

EVALUATION OF THERAPEUTIC OUTCOMES

- Initially, monitor anxious patients every 2 weeks for reduction in anxiety symptoms, improvement in functioning, and side effects. The Hamilton Rating Scale for Anxiety or the Sheehan Disability Scale can help measure drug response.
- Treatment resistance may be diagnosed after poor, partial, or lack of response is seen with at least two antidepressants from different classes. For those who do not achieve an appropriate response with a first-line agent the dose may be increased, changed to a different agent in the same class or different class, or augmented. If treatment fails, the clinician should assess for (a) symptoms (eg, psychotic symptoms) that need additional medications or (b) treatment nonadherence. Patients should also be assessed for concurrent substance use disorder, concurrent illnesses, and suicidal thoughts.

PANIC DISORDER: CLINICAL PRESENTATION

- Psychological symptoms include depersonalization (feeling detached from oneself); derealization (feelings of being detached from one's environment); and fear of losing control, going crazy, or dying.
- Physical symptoms include abdominal distress, chest pain or discomfort, chills, dizziness or lightheadedness, feeling of choking, heart sensations, nausea, palpitations, paresthesias, sensation of shortness or breath or smothering, sweating, tachycardia, and trembling or shaking.
- Recurrent unexpected panic attacks. At least one attack has been followed by at least 1 month of either or both (1) persistent worry about having another panic attack or their consequences or (2) maladaptive change in behavior related to the attacks.
- During an attack, there must be at least four symptoms in addition to intense fear or discomfort. Symptoms reach a peak within 10 minutes and usually last no more than 20 or 30 minutes.
- Up to 50% of Panic Disorder (PD) patients develop agoraphobia, which is marked fear or anxiety about being in at least 2 situations where escape could be difficult or help unavailable (eg, being in crowded places or crossing bridges). Patients may become homebound.

TREATMENT

- Goals of Treatment: Complete resolution of panic attacks, marked reduction in anticipatory anxiety, elimination of phobic avoidance, and no functional impairment.

Nonpharmacologic Therapy

- Cognitive Behavioral Therapy (CBT) is associated with short-term improvement in 80%–90% of patients and 6-month improvement in 75% of patients. Adding psychosocial treatment to pharmacotherapy may reduce likelihood of relapse when drug therapy is stopped.
- Educate patient to avoid caffeine, nicotine, alcohol, drugs of abuse, and stimulants. Aerobic exercise may benefit patients with PD.

Pharmacologic Therapy

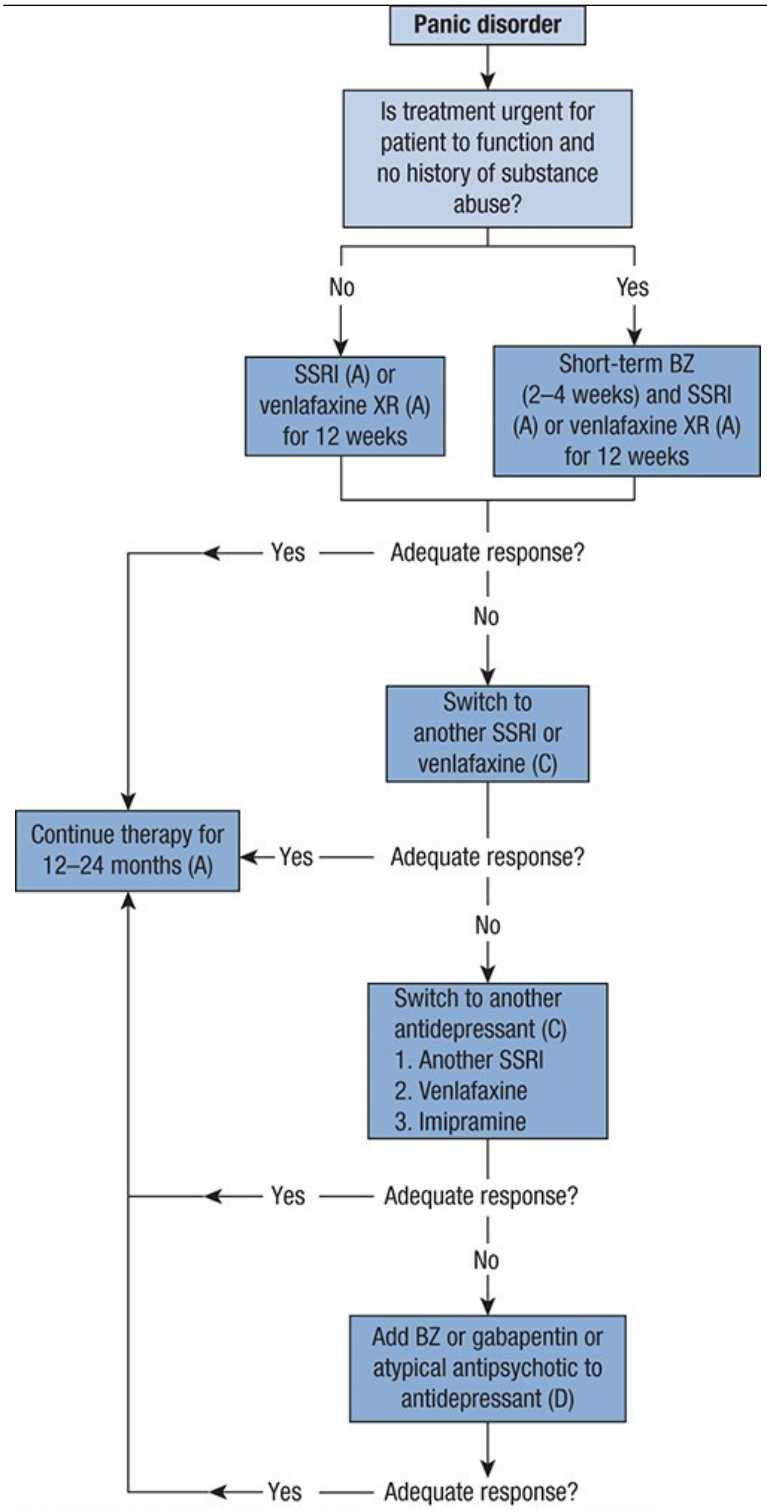
- SSRIs or **venlafaxine XR** are first-line agents for PD (**Table 66-7**), but benzodiazepines (second line agents) are the most commonly used drugs. **Imipramine** is considered second line. An algorithm for drug therapy of PD is shown in **Figure 66-2**.
- If pharmacotherapy is used, antidepressants, especially the SSRIs, are preferred in older patients and youth. The benzodiazepines are second line in these patients because of potential problems with disinhibition.
- The acute phase of treatment usually lasts 1–3 months with SSRIs. Therapy should be altered if there is no response after 6–8 weeks of an adequate dose. With benzodiazepines the acute phase lasts approximately 1 month.
- Usually patients are treated for 12–24 months before discontinuation is attempted over 4–6 months. Many patients require long-term therapy.

FIGURE 66-2

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); B, directly based on category II evidence (ie, at least one controlled study without randomization or one other type of quasi-experimental study); 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.)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 66-7

Drugs Used in the Treatment of Panic Disorder

Class/Generic Name	Brand Name	Starting Dose	Antipanic Dosage Range (mg)
SSRIs			
Citalopram	Celexa	10 mg/day	20–40
Escitalopram	Lexapro	5 mg/day	10–20
Fluoxetine	Prozac	5 mg/day	10–30
Fluvoxamine	Luvox	25 mg/day	100–300
Paroxetine	Paxil	10 mg/day	20–60
	Pexeva		
	Paxil CR	12.5 mg/day	25–75
Sertraline	Zoloft	25 mg/day	50–200
SNRI			
Venlafaxine XR	Effexor XR	37.5 mg/day	75–225
Benzodiazepines			
Alprazolam	Xanax	0.5 mg three times a day	4–10
	Xanax XR	0.5–1 mg/day	3–10
Clonazepam	Klonopin	0.25 mg once or twice daily	1–4
Diazepam	Valium	2–5 mg three times a day	5–20
Lorazepam	Ativan	0.5–1 mg three times a day	2–8
TCA			
Imipramine	Tofranil	10 mg/day	75–250
MAOI			
Phenelzine	Nardil	15 mg/day	45–90

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

Antidepressants

- **Citalopram** use is limited by QT prolongation.
- Stimulatory side effects (eg, anxiety, insomnia, and jitteriness) that can occur in tricyclic antidepressant (TCA) and SSRI-treated patients may hinder adherence and dose escalation. Low initial doses and gradual dose titration may eliminate these effects (see Table 66-7).
- Imipramine blocks panic attacks within 4 weeks in 75% of patients, but reducing anticipatory anxiety and phobic avoidance requires 8–12 weeks.
- Twenty-five percent of PD patients discontinue TCAs because of side effects.
- SSRIs eliminate panic attacks in 60%–80% of patients within about 4 weeks, but some patients require 8–12 weeks.
- Venlafaxine extended release is superior to placebo and similar in efficacy to **paroxetine** in relieving panic attacks, anticipatory anxiety, fear, and avoidance.

Benzodiazepines

- Benzodiazepines are second-line agents for PD except when rapid response is essential. Avoid benzodiazepine monotherapy in patients with PD who are depressed, have a history of depression, or a history of alcohol or drug abuse. They are often used concomitantly with antidepressants in the first 4–6 weeks to achieve a more rapid antipanic response.
- Relapse rates of 50% or higher are common despite slow drug tapering.
- **Alprazolam** and **clonazepam** are the preferred benzodiazepines for PD. Therapeutic response typically occurs within 1–2 weeks. The use of extended-release alprazolam or clonazepam avoids breakthrough symptoms between doses.

  ✔ A regular dosing schedule is preferred as the goal is to prevent panic attacks rather than reduce symptoms once an attack has already occurred

  ✔ The starting dose of clonazepam is 0.25 mg once or twice daily, with a dose increase of 0.25–0.5 mg every 3 days to 4 mg/day if needed.

  ✔ The starting dose of alprazolam is 0.25 three times daily (or 0.5 mg once daily of extended-release alprazolam), slowly increasing over several weeks as needed. Most patients require 3–6 mg/day.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate patients with PD every 1–2 weeks during the first few weeks to fine-tune dosing and to monitor side effects. Once stabilized, they can be seen every 2 months. The Panic Disorder Severity Scale (with a remission goal of three or less with no or mild agoraphobic avoidance, anxiety, disability, or depressive symptoms) and the Sheehan Disability Scale (with a goal of less than or equal to one on each item) can be used to measure disability. During drug discontinuation, the frequency of appointments should be increased.

POSTTRAUMATIC STRESS DISORDER: CLINICAL PRESENTATION

- In adults and children older than 6, there is exposure to actual or threatened death, serious injury, or sexual violence, either directly, or by witnessing the event(s) happening to others, learning about the event(s) happening to someone close, or experiencing repeated or extreme exposure to details of the event(s).
- Duration of intrusive, avoidance, alterations in thinking and mood, and hyperarousal symptoms (**Table 66-8**) must be present longer than 1 month and cause significant distress or impairment. There must be at least one intrusive symptom, one symptom of avoidance of stimuli associated with the trauma, at least two symptoms of negative alterations in thinking and mood, and at least two symptoms of increased arousal. PTSD co-occurs with mood, anxiety, and substance use disorders.

TABLE 66-8

Clinical Presentation of Posttraumatic Stress Disorder

Intrusion symptoms

- Recurrent, intrusive distressing memories of the trauma
- Recurrent, disturbing dreams of the event
- Feeling that the traumatic event is recurring (eg, dissociative flashbacks)
- Physiologic reaction to or psychological distress from reminders of the trauma

Avoidance symptoms

- Avoidance of conversations, thoughts, or feelings about the trauma
- Avoidance of people, places, or activities that are reminders of the event

Persistent negative alterations in thinking and mood

- Inability to recall an important aspect of the trauma
- Anhedonia
- Estrangement from others
- Restricted affect
- Negative beliefs about oneself
- Distorted beliefs causing one to blame others or themselves for the trauma
- Negative mood state

Hyperarousal symptoms

- Decreased concentration
- Easily startled
- Self-destructive behavior
- Hypervigilance
- Insomnia
- Irritability or anger outbursts

Specifiers

- Dissociative symptoms: depersonalization or derealization
- With delayed expression: full criteria are not met until at least 6 months posttrauma

TREATMENT

- Goals of Treatment: Reduction in core symptoms, disability, comorbidity and improved quality of life.
- Immediately after the trauma, patients should receive treatment individualized to their presenting symptoms (eg, nonbenzodiazepine hypnotic or short courses of trauma-focused cognitive behavioral therapy [CBT]). Brief courses of CBT in close proximity to the trauma can help prevent PTSD.
- If symptoms persist for 3–4 weeks, and there is social or occupational impairment, patients can receive pharmacotherapy or psychotherapy, or both.

Nonpharmacologic Therapy

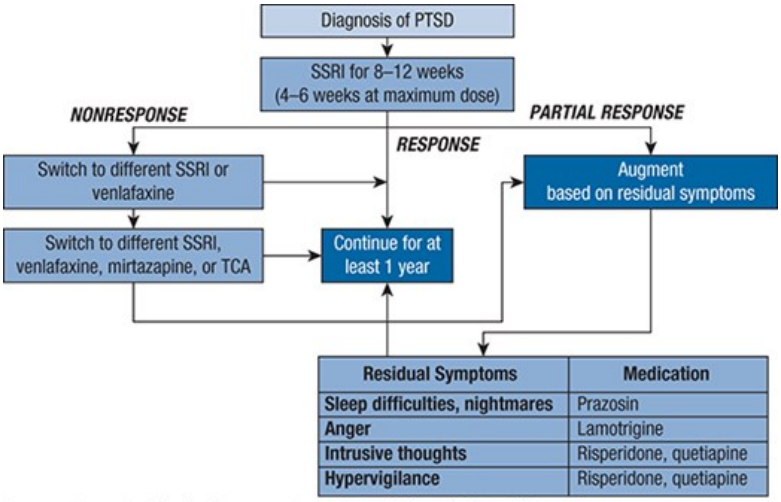
- Psychotherapies include stress management, eye movement desensitization and reprocessing (EMDR), and psychoeducation. Trauma-focused CBT and EMDR are more effective than stress management or group therapy to reduce PTSD symptoms.

Pharmacologic Therapy

- **Figure 66-3** shows an algorithm for the pharmacotherapy of PTSD.
- The SSRIs and venlafaxine are first-line pharmacotherapy for PTSD (**Table 66-9**). The TCAs and MAOIs also can be effective, but side effects can be problematic.
- **Sertraline** and **paroxetine** are approved for acute treatment of PTSD, and sertraline is approved for long-term management.
- Antiadrenergics and atypical antipsychotics can be used as augmenting agents.
- Large prospective studies document the effectiveness of sertraline and paroxetine in acute management of PTSD. Long-term use of SSRIs (9–12 months) was effective in preventing relapse.
- In a 12-week trial comparing **venlafaxine XR** and sertraline, venlafaxine XR was effective in reducing the avoidance/numbing and hyperarousal cluster, whereas sertraline improved all PTSD symptom clusters.
- **Mirtazapine,** amitriptyline and imipramine are second line drugs. **Phenelzine** is considered a third-line drug.
- If there is no improvement in the acute stress response 3–4 weeks following trauma, SSRIs should be started in a low dose with slow titration upward toward antidepressant doses. Eight to 12 weeks is an adequate duration of treatment to determine response.
- Responders to drug therapy should continue treatment for at least 12 months. When discontinued, drug therapy should be tapered slowly over 1 month or more to reduce the likelihood of relapse.
- **Prazosin,** in daily doses of 1–4 mg, can be useful in some patients with PTSD. It may be particularly helpful for nightmares and insomnia.
- **Risperidone, quetiapine,** α_1-adrenergic antagonists, antidepressants, mood stabilizers, and anticonvulsants may be used as augmenting agents in partial responders.

FIGURE 66-3

Algorithm for the pharmacotherapy of posttraumatic stress disorder (PTSD).



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 66-9

Dosing of Antidepressants in the Treatment of PTSD

Drug	Brand Name	Initial Dose	Usual Range (mg/day)
SSRIs			
Fluoxetine[a]	Prozac	10 mg/day	10–40[b]
Paroxetine[a]	Paxil, Pexeva	10–20 mg/day	20–40; max 50 mg/day[c]
Sertraline[a]	Zoloft	25 mg/day	50–100; max 200 mg/day[c]
Other agents			
Amitriptyline[a]	Elavil	25 or 50 mg/day	75–200[b]
Imipramine[a]	Tofranil	25 or 50 mg/day	75–200[b]
Mirtazapine[a]	Remeron	15 mg/night	30–60[b]
Phenelzine[a]	Nardil	15 or 30 mg every night	45–90[b]
Venlafaxine extended-release[a]	Effexor XR	37.5 mg/day	75–225[b]

[a]Available generically.

[b]Dosage used in clinical trials but not FDA approved.

[c]Dosage is FDA approved.

PTSD, posttraumatic stress disorder; SSRIs, selective serotonin reuptake inhibitors.

EVALUATION OF THERAPEUTIC OUTCOMES

- See patients frequently for the first 3 months, then monthly for 3 months. In months 6–12, patients can be seen every 2 months. Those who respond to pharmacotherapy should continue treatment for at least 12 months.
- Monitor for symptom response, suicidal ideation, disability, side effects, and treatment adherence. The Clinician-Administered PTSD Scale (CAPS) can be useful to assess symptom severity.

See Chapter 87, Anxiety Disorders: Generalized Anxiety, Panic, and Social Anxiety Disorders, authored by Sarah T. Melton and Cynthia K. Kirkwood, and Chapter 88, Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder, authored by Kristen N. Gardner, Jolene R. Bostwick, and Ericka L. Crouse, for a more detailed discussion of this topic.