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463 Psychiatric Disorders

Victor I. Reus

Psychiatric Disorders Psychiatric disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is ~30%, but only one-third of affected individuals are currently receiving treatment. Global burden of disease statistics indicates that 4 of the 10 most important causes of morbidity and attendant health care costs worldwide are psychiatric in origin. Changes in health care delivery underscore the need for primary care physicians to assume responsibility for the initial diagnosis and treatment of the most common mental disorders. Prompt diagnosis is essential to ensure that patients have access to appropriate medical services and to maximize the clinical outcome. Validated patient-based questionnaires have been developed that systematically probe for signs and symptoms associated with the most prevalent psychiatric diagnoses and guide the clinician into targeted assessment. The Primary Care Evaluation of Mental Disorders (PRIME-MD; and a self-report form, the Patient Health Questionnaire) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) are inventories that require only 10 min to complete and link patient responses to the formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence. A variety of smart phone apps for assessment and monitoring of psychiatric conditions and for psychological and pharmacologic treatment interventions are also available. A physician who refers patients to a psychiatrist should know not only when doing so is appropriate but also how to refer because societal misconceptions and the stigma of mental illness impede the process. Primary care physicians should base referrals to a psychiatrist on the presence of signs and symptoms of a mental disorder and not simply on the absence of a physical explanation for a patient's complaint. The physician should discuss with the patient the reasons for requesting the referral or consultation and provide reassurance that they will continue to provide medical care and work collaboratively with the mental health professional. Consultation with a psychiatrist or transfer of care is appropriate when physicians encounter evidence of psychotic symptoms, mania, severe depression, or anxiety; symptoms of post traumatic stress disorder (PTSD); suicidal or homicidal preoccupation; or a failure to respond to first-order treatment. This chapter reviews the clinical assessment and treatment of some of the most common mental disorders presenting in primary care and is based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), the framework for categorizing psychiatric illness used in the United States. Eating disorders are discussed later in this chapter, and the biology of psychiatric and addictive disorders is discussed in Chap. 462. ■

■GLOBAL CONSIDERATIONS The DSM-5-TR and the tenth revision of the International Classification of Diseases (ICD-10-CM), which is used more commonly world wide, have taken somewhat differing approaches to the diagnosis of mental illness, but considerable effort has been expended to provide an operational translation between the two nosologies. Both systems are in essence purely descriptive and emphasize clinical pragmatism, in distinction to the Research Domain Criteria (RDOC) proposed by the National Institute of Mental Health, which aspires to provide a causal framework for classification of behavioral disturbance. More recently, an alternative approach, based on a hierarchy of dimensions generated by factor analytic techniques, HiTOP (Hierarchical Taxonomy of Psychopathology) has been put forward as a possible improvement over DSM-5-TR for clinical usage, although it too lacks validity and is prone to diagnostic error. None of these diagnostic systems has as yet achieved adequate validation, and large-scale genetic investigations have revealed that differing psychiatric disorders overlap in their genetic risk variants and phenotypic symptoms. The Global Burden of

Disease Study (2019), using available epidemiologic data, nevertheless has reinforced the conclusion that, regardless of nosologic differences, mental and substance abuse disorders are the major cause of life-years lost to disability among all medical illnesses, affecting >300 million individuals worldwide. There is general agreement that high-income countries will need to build capacity in professional training in low- and middle-income countries in order to provide an adequate balanced care model for the delivery of evidence-based therapies for mental disorders. Recent surveys that indicate a dramatic increase in mental disorder prevalence in rapidly developing countries, such as China, may reflect both an increased recognition of the issue and also the consequence of social turmoil, stigma, and historically inadequate resources. A salient example of the ways in which societal disruption and isolation may contribute to exacerbating already unmet mental health needs can be seen in the COVID-19 pandemic, which resulted in an increased incidence of diagnosed psychiatric disorders in both affected and unaffected individuals, as well as caregivers. The need for improved prevention strategies and for more definitive and effective interventional treatments remains a global concern.

CHAPTER 463 ANXIETY DISORDERS Anxiety disorders, the most prevalent psychiatric illnesses in the general community, are present in 15–20% of medical clinic patients. Anxiety, defined as a subjective sense of unease, dread, or foreboding, can indicate a primary psychiatric condition or can be a component of, or reaction to, a primary medical disease. The primary anxiety disorders are classified according to their duration and course and the existence and nature of precipitants. Psychiatric Disorders When evaluating the anxious patient, the clinician must first determine whether the anxiety antedates or postdates a medical illness or is due to a medication side effect. Approximately one-third of patients presenting with anxiety have a medical etiology for their psychiatric symptoms, but an anxiety disorder can also present with somatic symptoms in the absence of a diagnosable medical condition. ■ ■PANIC DISORDER Clinical Manifestations Panic disorder is defined by the presence of recurrent and unpredictable panic attacks, which are distinct episodes of intense fear and discomfort associated with a variety of physical symptoms, including palpitations, sweating, trembling, shortness of breath, chest pain, dizziness, and a fear of impending doom or death. Paresthesias, gastrointestinal distress, and feelings of unreality are also common. Diagnostic criteria require at least 1 month of concern or worry about the attacks or a change in behavior related to them. The lifetime prevalence of panic disorder is 2–3%. Panic attacks have a sudden onset, developing within 10 min and usually resolving over the course of an

hour, and can occur in an unexpected fashion, such as when waking from sleep. The frequency and severity of panic attacks vary, ranging from once a week to clusters of attacks separated by months of well-being. The first attack is usually outside the home, and onset is typically in late adolescence to early adulthood. In some individuals, anticipatory anxiety develops over time and results in a generalized fear and a progressive avoidance of places or situations in which a panic attack might recur. Agoraphobia, which occurs commonly in patients with panic disorder, is an acquired irrational fear of being in places where one might feel trapped or unable to escape. It may, however, be diagnosed even if panic disorder is not present. Typically, it leads the patient into a progressive restriction in lifestyle and, in a literal sense, in geography. Frequently, patients are embarrassed that they are housebound and dependent on the company of others to go out into the world and do not volunteer this information; thus, physicians will fail to recognize the syndrome if direct questioning is not pursued. Differential Diagnosis A diagnosis of panic disorder is made after a medical etiology for the panic attacks has been ruled out. A variety of cardiovascular, respiratory, endocrine, and neurologic conditions can present with anxiety as the chief complaint. Patients with true panic disorder will often focus on one specific feature to the exclusion

of others. For example, 20% of patients who present with syncope as a primary medical complaint have a primary diagnosis of a mood, anxiety, or substance abuse disorder, the most common being panic disorder. The differential diagnosis of panic disorder is complicated by a high rate of comorbidity with other psychiatric conditions, especially alcohol and benzodiazepine abuse, which patients initially use in an attempt at self-medication. Some 75% of panic disorder patients will also satisfy criteria for major depression at some point in their illness.

When the history is nonspecific, physical examination and focused laboratory testing must be used to rule out anxiety states resulting from medical disorders such as pheochromocytoma, thyrotoxicosis, or hypoglycemia. Electrocardiogram (ECG) and echocardiogram may detect some cardiovascular conditions associated with panic, such as paroxysmal atrial tachycardia and mitral valve prolapse. In two studies, panic disorder was the primary diagnosis in 43% of patients with chest pain who had normal coronary angiograms and was present in 9% of all outpatients referred for cardiac evaluation. Panic disorder has also been diagnosed in many patients referred for pulmonary function testing or with symptoms of irritable bowel syndrome. PART 13 Neurologic Disorders Etiology and Pathophysiology The etiology of panic disorder is unknown but appears to involve a genetic predisposition, altered autonomic responsivity, and social learning. Panic disorder shows familial aggregation; the disorder is concordant in 30–45% of monozygotic twins, and genome-wide screens have identified suggestive risk loci. Acute panic attacks appear to be associated with increased noradrenergic discharges in the locus coeruleus. Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the α_2 -adrenergic antagonist yohimbine, cholecystokinin tetrapeptide (CCK-4), and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a pathway involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Resting-state functional magnetic resonance imaging (fMRI) has identified abnormalities in the default mode network involving the medial temporal lobe, with greater activation in the sensorimotor cortex in panic disorder and in amygdala-frontal connectivity in social anxiety disorder. TREATMENT Panic Disorder Patients with panic disorder have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the panic attack; accordingly, therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences, as well as preventing the

attack itself. Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medication (Tables 463-1 through 463-3). Selective serotonin reuptake inhibitors (SSRIs) benefit the majority of panic disorder patients and do not have the adverse effects of tricyclic antidepressants (TCAs). Fluoxetine, paroxetine, sertraline, and the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have received approval from the U.S. Food and Drug Administration (FDA) for this indication. These drugs should be started at one-third to one-half of their usual antidepressant dose (e.g., 5–10 mg fluoxetine, 25–50 mg sertraline, 10 mg paroxetine, venlafaxine 37.5 mg). Monoamine oxidase inhibitors (MAOIs) are also effective and may specifically benefit patients who have comorbid features of atypical depression (i.e., hypersomnia and weight gain). Insomnia, orthostatic hypotension, and the need to maintain a low-tyramine diet (avoidance of cheese and wine) have limited their use, however. Antidepressants typically take 2–6 weeks to become effective, and doses may need to be adjusted based on the clinical response. Because of anticipatory anxiety and the need for immediate relief of panic symptoms, benzodiazepines are useful early in the course of treatment and sporadically thereafter (Table 463-4). FDA-approved agents include alprazolam and clonazepam. A recent

Cochrane review found no difference between antidepressants and benzodiazepines in response rate, with desipramine and alprazolam ranked highest in achieving remission and clonazepam and alprazolam in reducing frequency of panic attacks. In treatment-resistant cases, short-term augmentation with aripiprazole, divalproex sodium, or pindolol has some evidence for efficacy. There also is no clear difference in short-term efficacy between psychological therapies and antidepressant or benzodiazepine treatment, alone or in combination. Early psychotherapeutic intervention and education aimed at symptom control enhance the effectiveness of drug treatment. Patients can be taught breathing techniques, be educated about physiologic changes that occur with panic, and learn to expose themselves voluntarily to precipitating events in a treatment program spanning 12–15 sessions. Homework assignments and monitored compliance are important components of successful treatment. Once patients have achieved a satisfactory response, drug treatment should be maintained for 1–2 years to prevent relapse. Controlled trials indicate a success rate of 75–85%, although the likelihood of complete remission is somewhat lower. ■ ■GENERALIZED ANXIETY DISORDER Clinical Manifestations Patients with generalized anxiety disorder (GAD) have persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic arousal, feeling “on edge” or restless, and insomnia (Table 463-5). Onset is usually before age 20 years, and a history of childhood fears and social inhibition may be present. The lifetime prevalence of GAD is 5–6%; the risk is higher in first-degree relatives of patients with the diagnosis. Interestingly, family studies indicate that GAD and panic disorder segregate independently. More than 80% of patients with GAD also suffer from major depression, dysthymia, or social phobia. Comorbid substance abuse is common in these patients, particularly alcohol and/or sedative/hypnotic abuse. Patients with GAD worry excessively over minor matters, with life-disrupting effects; unlike panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare. Etiology and Pathophysiology Most anxiogenic and anxiolytic agents act on the γ -aminobutyric acid (GABA)_A receptor/chloride ion channel complex, implicating this neurotransmitter system in pathogenesis. Benzodiazepines are thought to bind two separate GABA_A receptor sites: type I, which has a broad neuroanatomic distribution, and type II, which is concentrated in the hippocampus, striatum, and neocortex. The antianxiety effects of the various benzodiazepines are influenced by their relative binding to alpha

2 and 3 subunits of the GABAA receptor, and sedation and memory impairment to the alpha 1 subunit. Serotonin (5-hydroxytryptamine [5-HT]) and 3 α -reduced neuroactive steroids (allosteric modulators of GABAA) also appear to have a role in anxiety, and buspirone, a partial 5-HT1A receptor agonist, and certain 5-HT2A and 5-HT2C receptor antagonists (e.g., mirtazapine and nefazodone) may have beneficial effects. **TREATMENT Generalized Anxiety Disorder** A combination of pharmacologic and psychotherapeutic interventions is most effective in GAD, but complete symptomatic relief is rare. A short course of a benzodiazepine is usually indicated, preferably lorazepam, oxazepam, clonazepam, or alprazolam, although only the last two are FDA approved. (The first two of these agents are metabolized via conjugation rather than oxidation and thus do not accumulate if hepatic function is impaired; the latter also has limited active metabolites.) Treatment should be initiated at the lowest dose possible and prescribed on an as-needed basis as symptoms warrant. Benzodiazepines differ in their milligram per kilogram potency, half-life, lipid solubility, metabolic pathways, and presence of active metabolites. Agents that are absorbed rapidly and

TABLE 463-1 Antidepressants USUAL DAILY DOSE (mg) SIDE EFFECTS COMMENTS NAME SSRIs											
Fluoxetine (Prozac)	Sertraline (Zoloft)	Paroxetine (Paxil)	Fluvoxamine (Luvox)	Citalopram (Celexa)	Escitalopram (Lexapro)	10–80	50–200	20–60	100–300	20–60	10–30
Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other medicines (except sertraline); akathisia rare TCAs and Tetracyclics Amitriptyline (Elavil) Nortriptyline (Pamelor) Imipramine (Tofranil) Desipramine (Norpramin) Doxepin (Sinequan) Clomipramine (Anafranil) Maprotiline (Ludiomil) Protriptyline (Vivactil) Trimipramine (Surmontil) Amoxapine (Asendin)											
150–300	50–200	150–300	150–300	150–300	150–300	25–150	15–40	75–200	100–300		
Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain Nausea, anxiety, dry mouth Drowsiness, constipation, dry mouth Mixed Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) and Receptor Blockers Venlafaxine (Effexor), XR 75–375 Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia Desvenlafaxine (Pristiq) 50–400 Nausea, dizziness, insomnia Primary metabolite of venlafaxine; no increased efficacy with higher dosing Duloxetine (Cymbalta) 40–60 Nausea, dizziness, headache, insomnia, constipation Mirtazapine (Remeron) 15–45 Somnolence, weight gain; neutropenia rare Once-a-day dosing; 5-HT3 antagonist Vilazodone (Viibryd)											

Nausea, diarrhea, headache; dosage adjustment if given with CYP3A4 inhibitor/stimulator Vortioxetine (Trintellix) 5–20 Nausea, diarrhea, sweating, headache; low incidence of sedation or weight gain Levomilnacipran (Fetzima) 40–120 Nausea, constipation, sweating; rare increase in blood pressure/pulse Mixed-Action Drugs Bupropion (Wellbutrin), CR, XR 250–450 Jitteriness; flushing; seizures in at-risk patients; anorexia; tachycardia; psychosis Trazodone (Desyrel) 200–600 Sedation; dry mouth; ventricular irritability; postural hypotension; priapism rare Trazodone extended-release (Oleptro) 150–375 Daytime somnolence, dizziness, nausea Nefazodone Gepirone extended-release (Exxua) Esketamine (Spravato) Zuranolone (Zurzuvae) Dextromethorphan-bupropion (Auvelity) 300–600 18.2–72.6 56–84 1–2 times a week 50 qhs for 14 days 45/105 bid Headache, nausea, dizziness Dizziness, nausea, insomnia Sedation, dissociation, respiratory depression Somnolence, confusion, dizziness Dizziness, headache, diarrhea MAOIs Phenelzine (Nardil) Tranylcypromine (Parnate) 45–90 20–50 Insomnia; hypotension; edema; anorgasmia; weight gain; neuropathy; hypertensive crisis; toxic reactions with SSRIs;

narcotics Isocarboxazid (Marplan) 20–60 Less weight gain and hypotension than phenelzine
 Transdermal selegiline (Emsam) 6–12 Local skin reaction, hypertension No dietary restrictions with
 6-mg dose Abbreviations: ADD, attention-deficit disorder; EPS, extrapyramidal symptoms; FDA, U.S.
 Food and Drug Administration; GI, gastrointestinal; MAOIs, monoamine oxidase inhibitors; OCD,
 obsessive-compulsive disorder; OD, overdose; SSRIs, selective serotonin reuptake inhibitors; TCAs,
 tricyclic antidepressants.

Once-daily dosing, usually in the morning; fluoxetine has very long half-life; must not be combined
 with MAOIs Once-daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in
 overdose (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly CHAPTER 463 FDA-
 approved for OCD tid or qid dosing required Lethality in OD, EPS possible Psychiatric Disorders
 bid-tid dosing (extended-release available); lower potential for drug interactions than SSRIs;
 contraindicated with MAOIs May have utility in treatment of neuropathic pain and stress
 incontinence Also 5-HT_{1A} receptor partial agonist No specific p450 effects; 5-HT_{3A} and 5-HT₇
 receptor antagonist, 5-HT_{1B} partial agonist, and 5-HT_{1A} agonist Most noradrenergic of SNRIs tid
 dosing, but sustained-release also available; fewer sexual side effects than SSRIs or TCAs; may be
 useful for adult ADD Useful in low doses for sleep because of sedating effects with no
 anticholinergic side effects Rare risk of liver failure, priapism Partial agonist/5-HT_{1A}; 5-HT_{2A}
 antagonist Ketamine isomer for treatment-resistant depression and/or suicidal risk Oral
 neuroactive steroid for postpartum depression Possible increased speed of response May be more
 effective in patients with atypical features or treatment-refractory depression

TABLE 463-2 Management of Antidepressant Side Effects SYMPTOMS COMMENTS AND
 MANAGEMENT STRATEGIES Gastrointestinal Nausea, loss of Usually short-lived and dose-related;
 consider temporary dose reduction or administration with food and antacids appetite Diarrhea
 Famotidine, 20–40 mg/d Constipation Wait for tolerance; try diet change, stool softener, exercise;
 avoid laxatives Sexual dysfunction Consider dose reduction; drug holiday Anorgasmia/
 Bethanechol, 10–20 mg, 2 h before activity, or cyproheptadine, 4–8 mg, 2 h before activity, or
 bupropion, 100 mg bid, or amantadine, 100 mg bid/tid impotence; impaired ejaculation Orthostasis
 Tolerance unlikely; increase fluid intake, use calf exercises/support hose; fludrocortisone, 0.025
 mg/d Anticholinergic Wait for tolerance PART 13 Neurologic Disorders Dry mouth, eyes Maintain
 good oral hygiene; use artificial tears, sugar-free gum Tremor/jitteriness Antiparkinsonian drugs not
 effective; use dose reduction/ slow increase; lorazepam, 0.5 mg bid, or propranolol, 10–20 mg bid
 Insomnia Schedule all doses for the morning; trazodone, 50–100 mg qhs Sedation Caffeine;
 schedule all dosing for bedtime; bupropion, 75–100 mg in afternoon Headache Evaluate diet,
 stress, other drugs; try dose reduction; amitriptyline, 50 mg/d Weight gain Decrease
 carbohydrates; exercise; consider fluoxetine Loss of therapeutic benefit over time Related to
 tolerance? Increase dose or drug holiday; add amantadine, 100 mg bid, buspirone, 10 mg tid, or
 pindolol, 2.5 mg bid are lipid soluble, such as diazepam, have a rapid onset of action and a higher
 abuse potential. Benzodiazepines should generally not be prescribed for >4–6 weeks because of
 the development of tolerance and the serious risk of abuse and dependence. Withdrawal must be
 closely monitored as relapses can occur. It is important to warn patients that concomitant use of
 alcohol or other sedating drugs may exacerbate side effects and impair their ability to function. An
 optimistic approach that encourages the patient to clarify TABLE 463-4 Anxiolytics EQUIVALENT PO
 DOSE (mg) ONSET OF ACTION HALF-LIFE (h) COMMENTS NAME Benzodiazepines Diazepam (Valium)

Fast 20–70 Active metabolites; quite sedating Flurazepam (Dalmane)

Fast 30–100 Flurazepam is a prodrug; metabolites are active; quite sedating Triazolam (Halcion) 0.25 Intermediate 1.5–5 No active metabolites; can induce confusion and delirium, especially in elderly Lorazepam (Ativan)

Intermediate 10–20 No active metabolites; direct hepatic glucuronide conjugation; quite sedating; FDA-approved for anxiety with depression Alprazolam (Xanax) 0.5 Intermediate 12–15 Active metabolites; not too sedating; FDA-approved for panic disorder and anxiety with depression; tolerance and dependence develop easily; difficult to withdraw Chlordiazepoxide (Librium)

Intermediate 5–30 Active metabolites; moderately sedating Oxazepam (Serax)

Slow 5–15 No active metabolites; direct glucuronide conjugation; not too sedating Temazepam (Restoril)

Slow 9–12 No active metabolites; moderately sedating Clonazepam (Klonopin) 0.5 Slow 18–50 No active metabolites; moderately sedating; FDA-approved for panic disorder Clorazepate (Tranxene)

Fast 40–200 Low sedation; unreliable absorption Prazepam (Centrax) 10–60 Fast 29–224 Less sedating than diazepam Nonbenzodiazepines Buspirone (BuSpar) 7.5 2 weeks 2–3 Active metabolites; tid dosing—usual daily dose 10–20 mg tid; nonsedating; no additive effects with alcohol; useful for controlling agitation in demented or brain-injured patients Abbreviation: FDA, U.S. Food and Drug Administration.

TABLE 463-3 Possible Drug Interactions with Selective Serotonin Reuptake Inhibitors AGENT EFFECT Monoamine oxidase inhibitors Serotonin syndrome— absolute contraindication Serotonergic agonists, e.g., tryptophan, fenfluramine, triptans Potential serotonin syndrome Drugs that are metabolized by P450 isoenzymes: tricyclics, other SSRIs, antipsychotics, beta blockers, codeine, triazolobenzodiazepines, calcium channel blockers Delayed metabolism resulting in increased blood levels and potential toxicity Drugs that are bound tightly to plasma proteins, e.g., warfarin Increased bleeding secondary to displacement Drugs that inhibit the metabolism of SSRIs by P450 isoenzymes, e.g., quinidine Increased SSRI side effects Abbreviation: SSRIs, selective serotonin reuptake inhibitors. environmental precipitants, anticipate their reactions, and plan effective response strategies is an essential element of therapy. Adverse effects of benzodiazepines generally parallel their relative half-lives. Longer-acting agents, such as diazepam, chlordiazepoxide, flurazepam, and clonazepam, tend to accumulate active metabolites, with resultant sedation, impairment of cognition, and poor psychomotor performance. Shorter-acting compounds, such as alprazolam, lorazepam, and oxazepam, can produce daytime anxiety, early-morning insomnia, and, with discontinuation, rebound anxiety and insomnia. Although patients develop tolerance to the sedative effects of benzodiazepines, they are less likely to habituate to the adverse psychomotor effects. Withdrawal from the longer half-life benzodiazepines can be accomplished through gradual, stepwise dose reduction (by 10% every 1–2 weeks) over 6–12 weeks. It is usually more difficult to taper patients off shorter-acting benzodiazepines. Physicians may need to switch the patient to a benzodiazepine with a longer half-life or use an adjunctive medication such as a beta blocker or carbamazepine, before attempting to discontinue the

benzodiazepine. Withdrawal reactions vary in severity and duration; they can include depression, anxiety, lethargy, diaphoresis, autonomic arousal, and, rarely, seizures. Buspirone is a nonbenzodiazepine anxiolytic agent. It is non-sedating, does not produce tolerance or dependence, does not interact

TABLE 463-5 Diagnostic Criteria for Generalized Anxiety Disorder A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance). B. The individual finds it difficult to control the worry. C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): Note: Only one item is required in children. 1. Restlessness or feeling keyed up or on edge. 2. Being easily fatigued. 3. Difficulty concentrating or mind going blank. 4. Irritability. 5. Muscle tension. 6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep). D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism). F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder, contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder). Source: Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders-Text Revision, 5th ed. (Copyright © 2022). American Psychiatric Association. All Rights Reserved.

with benzodiazepine receptors or alcohol, and has no abuse or disinhibition potential. However, it requires several weeks to take effect and requires thrice-daily dosing. Patients who were previously responsive to a benzodiazepine are unlikely to rate buspirone as equally effective, but patients with head injury or dementia who have symptoms of anxiety and/or agitation may do well with this agent. Escitalopram, paroxetine, duloxetine, and venlafaxine are FDA approved for the treatment of GAD, usually at doses that are comparable to their efficacy in major depression, and may be preferable to usage of benzodiazepines in the treatment of chronic anxiety. Benzodiazepines are contraindicated during pregnancy and breastfeeding. Anticonvulsants with GABAergic properties may also be effective against anxiety. Gabapentin, oxcarbazepine, tiagabine, pregabalin, and divalproex have all shown some degree of benefit in a variety of anxiety-related syndromes in off-label usage. ■ ■

PHOBIC DISORDERS

Clinical Manifestations The cardinal feature of phobic disorders is a marked and persistent fear of objects or situations, exposure to which results in an immediate anxiety reaction. The patient avoids the phobic stimulus, and this avoidance usually impairs occupational or social functioning. Panic attacks may be triggered by the phobic stimulus or may occur spontaneously. Unlike patients with other anxiety disorders, individuals with phobias usually experience anxiety only in specific situations. Common phobias include fear of closed spaces (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others. Examples include having to converse at a party, using public restrooms, or meeting strangers. In each case, the affected individual is aware that the experienced fear is excessive and

unreasonable given the circumstance. The specific content of a phobia may vary across gender, ethnic, and cultural boundaries.

Phobic disorders are common, affecting ~7–9% of the population. Twice as many females are affected than males. Full criteria for diagnosis are usually satisfied first in early adulthood, but behavioral avoidance of unfamiliar people, situations, or objects dating from early childhood is common.

In one study of female twins, concordance rates for agoraphobia, social phobia, and animal phobia were found to be 23% for monozygotic twins and 15% for dizygotic twins. A twin study of fear conditioning, a model for the acquisition of phobias, demonstrated a heritability of 35–45%. Animal studies of fear conditioning have indicated that processing of the fear stimulus occurs through the lateral nucleus of the amygdala, extending through the central nucleus and projecting to the periaqueductal gray region, lateral hypothalamus, and paraventricular hypothalamus.

TREATMENT

Phobic Disorders

CHAPTER 463 Beta blockers (e.g., propranolol, 20–40 mg orally 2 h before the event) are particularly effective in the treatment of “performance anxiety” (but not general social phobia) and appear to work by blocking the peripheral manifestations of anxiety such as perspiration, tachycardia, palpitations, and tremor. MAOIs alleviate social phobia independently of their antidepressant activity, and paroxetine, sertraline, fluvoxamine CR, and venlafaxine XR have received FDA approval for treatment of social anxiety. Benzodiazepines can be helpful in reducing fearful avoidance, but the chronic nature of phobic disorders limits their usefulness. Psychiatric Disorders Behaviorally focused psychotherapy is an important component of treatment because relapse rates are high when medication is used as the sole treatment. Cognitive-behavioral strategies are based on the finding that distorted perceptions and interpretations of fear-producing stimuli play a major role in perpetuation of phobias. Individual and group therapy sessions teach the patient to identify specific negative thoughts associated with the anxiety-producing situation and help to reduce the patient’s fear of loss of control. In desensitization therapy, hierarchies of feared situations are constructed, and the patient is encouraged to pursue and master gradual exposure to the anxiety-producing stimuli. Patients with social phobia, in particular, have a high rate of comorbid alcohol abuse, as well as of other psychiatric conditions (e.g., eating disorders), necessitating the need for parallel management of each disorder if anxiety reduction is to be achieved. ■ ■

STRESS DISORDERS Clinical Manifestations Patients may develop anxiety after exposure to extreme traumatic events such as the threat of personal death or injury or the death of a loved one. The reaction may occur shortly after the trauma (acute stress disorder) or be delayed and subject to recurrence (PTSD) (Table 463-6). In both syndromes, individuals experience associated symptoms of detachment and loss of emotional responsiveness. The patient may feel depersonalized and unable to recall specific aspects of the trauma, although typically, it is reexperienced through intrusions in thought, dreams, or flashbacks, particularly when cues of the original event are present. Patients often actively avoid stimuli that precipitate recollections of the trauma and demonstrate a resulting increase in vigilance, arousal, and startle response. Patients with stress disorders are at risk for the development of other disorders related to anxiety, mood, and substance abuse (especially alcohol). Between 5 and 10% of Americans will at some time in their life satisfy criteria for PTSD, with women more likely to be affected than men. A validated four-item screen for PTSD (PC-PTSD) is available. Risk factors for the development of PTSD include a past psychiatric history and personality characteristics of high neuroticism and extroversion. Twin studies show a substantial genetic influence on all symptoms associated with PTSD, with less

evidence for an environmental effect.

PART 13 Neurologic Disorders TABLE 463-6 Diagnostic Criteria for Posttraumatic Stress Disorder
Posttraumatic Stress Disorder in Individuals Older Than 6 Years Note: The following criteria apply to adults, adolescents, and children older than 6 years. For children 6 years and younger, see corresponding criteria below. A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. Directly experiencing the traumatic event(s). 2. Witnessing, in person, the event(s) as it occurred to others. 3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
2. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related. B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
3. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
4. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s). Note: In children, there may be frightening dreams without recognizable content.
5. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play.
6. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). 5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
7. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s). 2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s). D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
8. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
9. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined"). 3. Persistent, distorted cognitions

about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others. 4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame). 5. Markedly diminished interest or participation in significant activities. 6. Feelings of detachment or estrangement from others. 7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings). E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

10. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects. 2. Reckless or self-destructive behavior. 3. Hypervigilance. 4. Exaggerated startle response. 5. Problems with concentration. 6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep). F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month. G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition. Specify whether: With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following: 1. 1. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
11. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted). 2. Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures). Specify if: With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate). Posttraumatic Stress Disorder in Children 6 Years and Younger A. In children 6 years and younger, exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
12. Directly experiencing the traumatic event(s). 2. Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers. 3. Learning that the traumatic event(s) occurred to a parent or caregiving figure. B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
13. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: Spontaneous and intrusive memories may not necessarily appear distressing and may be expressed as play reenactment.
14. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s). Note: It may not be possible to ascertain that the frightening content is related to the traumatic event.
15. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most

extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play. 4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). 5. Marked physiological reactions to reminders of the traumatic event(s). C. One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s): Persistent Avoidance of Stimuli

16. Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections of the traumatic event(s).
2. Avoidance of or efforts to avoid people, conversations, or interpersonal situations that arouse recollections of the traumatic event(s).

(Continued)

TABLE 463-6 Diagnostic Criteria for Posttraumatic Stress Disorder Negative Alterations in Cognitions

3. Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
4. Markedly diminished interest or participation in significant activities, including constriction of play.
5. Socially withdrawn behavior.
6. Persistent reduction in expression of positive emotions.

D. Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects (including extreme temper tantrums).
 2. Hypervigilance.
 3. Exaggerated startle response.
 4. Problems with concentration.
 5. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).
- E. The duration of the disturbance is more than 1 month. F. The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior. G. The disturbance is not attributable to the physiological effects of a substance (e.g., medication or alcohol) or another medical condition. Specify whether: With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:
2. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
 2. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts) or another medical condition (e.g., complex partial seizures). Specify if: With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate). Source: Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders-Text Revision, 5th ed. (Copyright © 2022). American Psychiatric Association. All Rights Reserved. Etiology and Pathophysiology It is hypothesized that in PTSD there is excessive release of norepinephrine from the locus coeruleus in response to stress and increased

noradrenergic activity at projection sites in the hippocampus and amygdala. These changes theoretically facilitate the encoding of fear-based memories. Greater sympathetic responses to cues associated with the traumatic event occur in PTSD, although pituitary adrenal responses are blunted. In addition to fear learning, changes in threat detection (insula overactivity), executive function, emotional regulation, and contextual learning have been documented. Predictive biomarkers include increased heart rate and serum lactate, decreased coagulation, insulin resistance, and alterations in glycolysis and fatty acid uptake.

TREATMENT Stress Disorders Acute stress reactions are usually self-limited, and treatment typically involves the short-term use of benzodiazepines and supportive/expressive psychotherapy. The chronic and recurrent nature of PTSD, however, requires a more complex approach using drug and behavioral treatments. PTSD is highly correlated with peritraumatic dissociative symptoms and the development of an acute stress disorder at the time of the trauma. Attempts to prevent or ameliorate PTSD through usage of agents such as escitalopram, hydrocortisone, and intranasal oxytocin in the acute stress period have proven equivocal. The SSRIs (paroxetine and sertraline are FDA approved for PTSD), venlafaxine, fluoxetine, and topiramate can all reduce anxiety, symptoms of intrusion, and avoidance behaviors. Recently, the psychedelic agent MDMA (3,4-methylenedioxymethamphetamine) demonstrated efficacy as an adjunct to intensive psychotherapeutic intervention, as did stellate ganglion block. Low-dose trazodone and mirtazapine, sedating antidepressants, are frequently used at night to help with insomnia. Benzodiazepines and SSRIs, however, should not be given in the early aftermath of trauma. Psychotherapeutic strategies for PTSD help the patient overcome avoidance behaviors and demoralization and master fear of recurrence of the trauma; therapies that encourage the patient to dismantle avoidance behaviors through stepwise focusing on the experience of the traumatic event, such as trauma-focused cognitive-behavioral and eye movement desensitization and reprocessing (EMDR) therapies and prolonged exposure therapy utilizing augmented or virtual reality are the most effective. Debriefing after the traumatic event does not prevent PTSD and may exacerbate symptoms.

(Continued) CHAPTER 463 Psychiatric Disorders ■ ■ **OBSESSIVE-COMPULSIVE DISORDER** Clinical Manifestations Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive behaviors that impair everyday functioning. Fears of contamination and germs are common, as are handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked. The degree to which the disorder is disruptive for the individual varies, but in all cases, obsessive-compulsive activities take up >1 h per day and are undertaken to relieve the anxiety triggered by the core fear. Patients often conceal their symptoms, usually because they are embarrassed by the content of their thoughts or the nature of their actions. Physicians must ask specific questions regarding recurrent thoughts and behaviors, particularly if physical clues such as chafed and reddened hands or patchy hair loss (from repetitive hair pulling, or trichotillomania) are present. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. OCD has a lifetime prevalence of 2–3% worldwide. Onset is usually gradual, beginning in early adulthood, but childhood onset is not rare. The disorder usually has a waxing and waning course, but some cases may show a steady deterioration in psychosocial functioning. Etiology and Pathophysiology A genetic contribution to OCD is suggested by twin studies, but no susceptibility gene for OCD has been identified to date. Insulin signaling has been implicated in some recent reports. Family studies show an aggregation

of OCD with Tourette's disorder, and both are more common in males and in first-born children. The anatomy of obsessive-compulsive behavior is thought to include the orbital frontal cortex, caudate nucleus, and globus pallidus. The caudate nucleus appears to be involved in the acquisition and maintenance of habit and skill learning, and interventions that are successful in reducing obsessive-compulsive behaviors also decrease metabolic activity in the caudate. **TREATMENT** Obsessive-Compulsive Disorder Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are approved for the treatment of OCD in adults (and all but paroxetine are also approved for children). Clomipramine is a TCA that is often tolerated poorly owing to anticholinergic and sedative side effects at the doses required to treat the illness (25–250 mg/d); its efficacy in OCD is unrelated to its antidepressant activity.

Fluoxetine (5–60 mg/d), fluvoxamine (25–300 mg/d), paroxetine (40–60 mg/d), and sertraline (50–150 mg/d) are as effective as clomipramine and have a more benign side effect profile. Venlafaxine and duloxetine also have shown efficacy but are not FDA approved. Only 50–60% of patients with OCD show adequate improvement with pharmacotherapy alone. In treatment-resistant cases, augmentation with other serotonergic agents such as buspirone, or with a neuroleptic or benzodiazepine, may be beneficial, or alternatively, high-dose theta burst repetitive transcranial magnetic stimulation (rTMS). In severe cases, closed loop deep-brain stimulation has been found to be effective. When a therapeutic response is achieved, long-duration maintenance therapy is usually indicated.

For many individuals, particularly those with time-consuming compulsions, behavior therapy and exposure response prevention will result in as much improvement as that afforded by medication. Effective techniques include the gradual increase in exposure to stressful situations, maintenance of a diary to clarify stressors, and homework assignments that substitute new activities for compulsive behaviors. **PART 13 Neurologic Disorders MOOD DISORDERS** Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect. Mood disorders are subdivided into (1) depressive disorders, (2) bipolar disorders, and (3) depression in association with medical illness or alcohol and substance abuse (Chaps. 464 through 468). Major depressive disorder (MDD) is differentiated from bipolar disorder by the absence of a manic or hypomanic episode. The relationship between pure depressive syndromes and bipolar disorders is not well understood; MDD is more frequent in families of bipolar individuals, but the reverse is not true. In the most recent Global Burden of Disease Study conducted by the World Health Organization (2019), depression was the single largest factor contributing to disability, which had increased 61% as measured by disability-adjusted life-years (DALYs) since 1990. In the United States, lost productivity directly related to mood disorders has been estimated at \$55.1 billion per year. ■ **■DEPRESSION IN ASSOCIATION WITH MEDICAL ILLNESS** Depression occurring in the context of medical illness is difficult to evaluate. Depressive symptomatology may reflect the psychological stress of coping with the disease, may be caused by the disease process itself or by the medications used to treat it, or may simply coexist in time with the medical diagnosis. Virtually every class of medication includes some agent that can induce depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Iatrogenic depression should also be considered in patients receiving glucocorticoids, antimicrobials, systemic analgesics, anti-parkinsonian medications, and anticonvulsants. To decide whether a causal relationship exists between pharmacologic therapy and a patient's change in mood, it may sometimes be necessary to undertake an empirical trial of an alternative medication.

Between 20 and 30% of cardiac patients manifest a depressive disorder; an even higher percentage experience depressive symptomatology when self-reporting scales are used. Depressive symptoms following unstable angina, myocardial infarction, cardiac bypass surgery, or heart transplant impair rehabilitation and are associated with higher rates of mortality and medical morbidity. Depressed patients often show decreased variability in heart rate (an index of reduced parasympathetic nervous system activity), which may predispose individuals to ventricular arrhythmia and increased morbidity. Depression also appears to increase the risk of coronary heart disease, possibly through increased platelet aggregation. TCAs are contraindicated in patients with bundle branch block, and TCA-induced tachycardia is an additional concern in patients with congestive heart failure. SSRIs appear not to induce ECG changes or adverse cardiac events and thus are reasonable first-line drugs for patients at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

In patients with cancer, the mean prevalence of depression is 25%, but depression occurs in 40–50% of patients with cancers of the pancreas or oropharynx. This association is not due to the effect of cachexia alone, as the higher prevalence of depression in patients with pancreatic cancer persists when compared to those with advanced gastric cancer. Initiation of antidepressant medication in cancer patients has been shown to improve quality of life as well as mood. Psychotherapeutic approaches, particularly group therapy, may have some effect on short-term depression, anxiety, and pain symptoms. Depression occurs frequently in patients with neurologic disorders, particularly cerebrovascular disorders, Parkinson's disease, dementia, multiple sclerosis, and traumatic brain injury. One in five patients with left-hemisphere stroke involving the dorsolateral frontal cortex experiences major depression. Late-onset depression in otherwise cognitively normal individuals increases the risk of a subsequent diagnosis of Alzheimer's disease. All classes of antidepressant agents are effective against these depressions, as are, in some cases, stimulant compounds. SNRIs such as duloxetine or levomilnacipran may be more effective in depression associated with chronic pain. The reported prevalence of depression in patients with diabetes mellitus varies from 8 to 27%, with the severity of the mood state correlating with the level of hyperglycemia and the presence of diabetic complications. Treatment of depression may be complicated by effects of antidepressive agents on glycemic control. MAOIs can induce hypoglycemia and weight gain, whereas TCAs can produce hyperglycemia and carbohydrate craving. SSRIs and SNRIs, like MAOIs, may reduce fasting plasma glucose but are easier to use and may also improve dietary and medication compliance. Hypothyroidism is frequently associated with features of depression, most commonly depressed mood and memory impairment. Hyperthyroid states may also present in a similar fashion, usually in geriatric populations. Improvement in mood usually follows normalization of thyroid function, but adjunctive antidepressant medication is sometimes required. Patients with subclinical hypothyroidism can also experience symptoms of depression and cognitive difficulty that respond to thyroid replacement. The lifetime prevalence of depression in HIV-positive individuals has been estimated at 22–45%. The relationship between depression and disease progression is multifactorial and likely to involve psychological and social factors, alterations in immune function, and central nervous system (CNS) disease. Chronic hepatitis C infection is also associated with depression, which may worsen with interferon- α treatment. Some chronic disorders of uncertain etiology, such as chronic fatigue syndrome (Chap. 461) and fibromyalgia (Chap. 385), are strongly associated with depression and anxiety; patients may benefit from antidepressant treatment or anticonvulsant agents such as pregabalin. ■

■ **DEPRESSIVE DISORDERS Clinical Manifestations** Major depression is defined as depressed mood

on a daily basis for a minimum duration of 2 weeks (Table 463-7). An episode may be characterized by sadness, indifference, apathy, or irritability and is usually associated with changes in sleep patterns, appetite, and weight; motor agitation or retardation; fatigue; impaired concentration and decision-making; feelings of shame or guilt; and thoughts of death or dying. Patients with depression have a profound loss of pleasure in all enjoyable activities, exhibit early-morning awakening, feel that the dysphoric mood state is qualitatively different from sadness, and often notice a diurnal variation in mood (worse in morning hours). Patients experiencing bereavement or grief may exhibit many of the same signs and symptoms of major depression, although the emphasis is usually on feelings of emptiness and loss, rather than anhedonia and loss of self-esteem, and the duration is usually limited. In certain cases, however, the diagnosis of major depression may be warranted even in the context of a significant loss. Approximately 15% of the population experiences a major depressive episode at some point in life, and 6–8% of all outpatients in

TABLE 463-7 Criteria for a Major Depressive Episode A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.) 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. C. The episode is not attributable to the physiological effects of a substance or another medical condition. Note: Criteria A–C represent a major depressive episode. Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.¹ D. At least one major depressive episode is not better explained by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders. E. There has never been a manic episode or a hypomanic episode. Note: This exclusion

does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition. 1In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in an MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of an MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of an MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in an MDE. In grief, self-esteem is generally preserved, whereas in an MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about “joining” the deceased, whereas in an MDE such thoughts are focused on ending one’s own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression. Source: Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders-Text Revision, 5th ed. (Copyright © 2022). American Psychiatric Association. All Rights Reserved.

primary care settings satisfy diagnostic criteria for the disorder. Depression is often undiagnosed and, even more frequently, is treated inadequately. If a physician suspects the presence of a major depressive episode, the initial task is to determine whether it represents unipolar or bipolar depression or is one of the 10–15% of cases that are secondary to general medical illness or substance abuse. Physicians should also assess the risk of suicide by direct questioning, as patients are often reluctant to verbalize such thoughts without prompting. If specific plans are uncovered or if significant risk factors exist (e.g., a past history of suicide attempts, profound hopelessness, concurrent medical illness, substance abuse, or social isolation), the patient must be referred to a mental health specialist for immediate care. The physician should specifically probe each of these areas in an empathic and hopeful manner, being sensitive to denial and possible minimization of distress. The presence of anxiety, panic, or agitation significantly increases near-term suicidal risk. Approximately 4–5% of all depressed patients will commit suicide; most will have sought help from physicians within 1 month of their deaths.

CHAPTER 463 In some depressed patients, the mood disorder does not appear to be episodic and is not clearly associated with either psychosocial dysfunction or change from the individual’s usual experience in life. Persistent depressive disorder (dysthymic disorder) consists of a pattern of chronic (at least 2 years), ongoing depressive symptoms that are usually less severe and/or less numerous than those found in major depression, but the functional consequences may be equivalent to or even greater; the two conditions are sometimes difficult to separate and can occur together (“double depression”). Many patients who exhibit a profile of pessimism, disinterest, and low self-esteem respond to antidepressant treatment. Persistent and chronic depressive disorders occur in ~2% of the general population. Psychiatric Disorders Depression is approximately twice as common in women as in men, and the incidence increases with age in both sexes. Twin studies indicate that the liability to major depression of early onset (before age 25 years) is largely genetic

in origin. Negative life events can precipitate and contribute to depression, but genetic factors influence the sensitivity of individuals to these stressful events. In most cases, both biologic and psychosocial factors are involved in the precipitation and unfolding of depressive episodes. The most potent stressors appear to involve death of a relative, assault, or severe marital or relationship problems. Unipolar depressive disorders usually begin in early adulthood and recur episodically over the course of a lifetime. The best predictor of future risk is the number of past episodes; 50–60% of patients who have a first episode have at least one or two recurrences. Some patients experience multiple episodes that become more severe and frequent over time. The duration of an untreated episode varies greatly, ranging from a few months to ≥ 1 year. The pattern of recurrence and clinical progression in a developing episode are also variable. Within an individual, the nature of episodes (e.g., specific presenting symptoms, frequency, and duration) may be similar over time. In a minority of patients, a severe depressive episode can progress to a psychotic state, and in elderly patients, depressive symptoms can be associated with cognitive deficits mimicking dementia (“pseudodementia”). A seasonal pattern of depression, called seasonal affective disorder, may manifest with onset and remission of episodes at predictable times of the year. This disorder is more common in women, with symptoms of anergy, fatigue, weight gain, hypersomnia, and episodic carbohydrate craving. The prevalence increases with distance from the equator, and improvement may occur by altering light exposure.

Etiology and Pathophysiology

Although evidence for genetic transmission of unipolar depression is not as strong as in bipolar disorder, monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%), with little support for any effect of a shared family environment. Large-scale genome-wide association studies (GWAS) involving hundreds of thousands of cases and controls have identified several hundred loci across the genome, some of which are unique to major depression, but others of which overlap with findings from disparate psychiatric disorders, indicating possible pleiotropy. Epigenetic changes are also likely to contribute to risk.

Neuroendocrine abnormalities that reflect the neurovegetative signs and symptoms of depression include increased cortisol and corticotropin-releasing hormone (CRH) secretion, a decreased inhibitory response of glucocorticoids to dexamethasone, and a blunted response of thyroid-stimulating hormone (TSH) level to infusion of thyroid-releasing hormone (TRH). Antidepressant treatment leads to normalization of these abnormalities. Major depression is also associated with changes in levels of proinflammatory cytokines and neurotrophins, an increase in measures of oxidative stress and cellular aging, telomere shortening, epigenetic changes, and mitochondrial dysfunction. Alterations in the gut microbiome may also be involved.

Diurnal variations in symptom severity and alterations in circadian rhythmicity of a number of neurochemical and neurohumoral factors suggest that a primary defect may be present in regulation of biologic rhythms. Patients with major depression show consistent findings of a decrease in rapid eye movement (REM)–sleep onset (REM latency), an increase in REM density, and, in some subjects, a decrease in stage IV delta slow-wave sleep.

PART 13 Neurologic Disorders

Although antidepressant drugs inhibit neurotransmitter uptake within hours, their therapeutic effects typically emerge over several weeks, implicating adaptive changes in second messenger systems and neurotrophic and transcription factors as possible mechanisms of action.

TREATMENT

Depressive Disorders Treatment planning requires coordination of short-term strategies to induce remission combined with longer-term maintenance designed to prevent recurrence. The most effective intervention for achieving remission and preventing relapse is medication, but combined

treatments, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improve outcomes, as do self-help strategies such as exercise (Fig. 463-1). Approximately 40% of primary care patients with depression drop out of treatment and discontinue medication if symptomatic. Determine whether there is a history of good response to a medication in the patient or a first-degree relative; if yes, consider treatment with this agent if compatible with considerations in step 2. Evaluate patient characteristics and match to drug; consider health status, side effect profile, convenience, cost, patient preference, drug interaction risk, suicide potential, and medication compliance history. Begin new medication at 1/3 to 1/2 target dose if drug is a TCA, bupropion, venlafaxine, or mirtazapine, or full dose as tolerated if drug is an SSRI. If problem side effects occur, evaluate possibility of tolerance; consider temporary decrease in dose or adjunctive treatment. If unacceptable side effects continue, taper drug over 1 week and initiate new trial; consider potential drug interactions in choice. Evaluate response after 6 weeks at target dose; if response is inadequate, increase dose in stepwise fashion as tolerated. If inadequate response after maximal dose, consider tapering and switching to a new drug vs adjunctive treatment; if drug is a TCA, obtain plasma level to guide further treatment. FIGURE 463-1 A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Improvement is not noted within a month, unless additional support is provided. Outcome improves with (1) increased intensity and frequency of visits during the first 4–6 weeks of treatment, (2) supplemental educational materials, and (3) psychiatric consultation as indicated. Despite the widespread use of SSRIs and other second-generation antidepressant drugs, there is no convincing evidence that these classes of antidepressants are more efficacious than TCAs. Between 60 and 70% of all depressed patients respond to any drug chosen, if it is given in a sufficient dose for 6–8 weeks. A rational approach to selecting which antidepressant to use (Table 463-1) involves matching the patient's preference and medical history with the metabolic and side effect profile of the drug (Tables 463-2 and 463-3). A previous response, or a family history of a positive response, to a specific antidepressant often suggests that drug should be tried first. Before initiating antidepressant therapy, the physician should evaluate the possible contribution of comorbid illnesses and consider their specific treatment. In individuals with suicidal ideation, particular attention should be paid to choosing a drug with low toxicity if taken in overdose. Newer antidepressant drugs are distinctly safer in this regard; nevertheless, the advantages of TCAs have not been completely superseded. The existence of generic equivalents makes TCAs relatively cheap, and for secondary tricyclics, particularly nortriptyline and desipramine, well-defined relationships among dose, plasma level, and therapeutic response exist. The steady-state plasma level achieved for a given drug dose can vary more than tenfold between individuals, and plasma levels may help in interpreting apparent resistance to treatment and/or unexpected drug toxicity. The principal side effects of TCAs are antihistaminergic (sedation) and anticholinergic (constipation, dry mouth, urinary hesitancy, blurred vision). TCAs are contraindicated in patients with serious cardiovascular risk factors, and overdoses of tricyclic agents can be lethal, with desipramine carrying the greatest risk. It is judicious to prescribe only a 10-day supply when suicide is a risk. Most patients require a daily dose of 150–200 mg of imipramine or amitriptyline or its equivalent to achieve a therapeutic blood level of 150–300 ng/mL and a satisfactory remission; some patients show a partial effect at lower doses. Geriatric patients may require a low starting dose and slow escalation. Ethnic differences in drug metabolism are significant, with Hispanic, Asian, and black patients generally requiring lower doses to achieve a comparable blood level.

Second-generation antidepressants are similar to tricyclics in their effect on neurotransmitter reuptake, although some also have specific actions on catecholamine and indolamine receptors as well. Amoxapine is a dibenzoxazepine derivative that blocks norepinephrine and serotonin reuptake and has a metabolite that shows a degree of dopamine blockade. Long-term use of this drug carries a risk of tardive dyskinesia. Maprotiline is a potent norad renergic reuptake blocker that has little anticholinergic effect but may produce seizures. Bupropion is a novel antidepressant whose mechanism of action is thought to involve enhancement of norad renergic function. It has no anticholinergic, sedating, or orthostatic side effects and has a low incidence of sexual side effects. It may, however, be associated with stimulant-like side effects, may lower seizure threshold, and has an exceptionally short half-life, requiring frequent dosing. An extended-release preparation is available, as is a version combining it with dextromethorphan, an N-methyl-D-aspartate (NMDA) receptor agonist, that is proposed to result in a more rapid therapeutic response. SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram cause a lower frequency of anticholinergic, sedating, and cardiovascular side effects but a possibly greater incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than do TCAs. Akathisia, involving an inner sense of restlessness and anxiety in addition to increased motor activity, may also be more common, particularly during the first week of treatment. One concern is the risk of "serotonin syndrome," which is thought to result from hyperstimulation of brainstem 5-HT_{1A} receptors and is characterized by myoclonus, agitation, abdominal cramping, hyperpyrexia,

hypertension, and potentially death. Serotonergic agonists taken in combination should be monitored closely for this reason. Considerations such as half-life, compliance, toxicity, and drug-drug interactions may guide the choice of a particular SSRI. Fluoxetine and its principal active metabolite, norfluoxetine, for example, have a combined half-life of almost 7 days, resulting in a delay of 5 weeks before steady-state levels are achieved and a similar delay for complete drug excretion once their use is discontinued; paroxetine appears to incur a greater risk of withdrawal symptoms with abrupt discontinuation. All the SSRIs may impair sexual function, resulting in diminished libido, impotence, or difficulty in achieving orgasm. Sexual dysfunction frequently results in noncompliance and should be asked about specifically. Sexual dysfunction can sometimes be ameliorated by lowering the dose, by instituting weekend drug holidays (two or three times a month), or by treatment with amantadine (100 mg tid), bethanechol (25 mg tid), buspirone (10 mg tid), or bupropion (100–150 mg/d). Paroxetine appears to be more anticholinergic than either fluoxetine or sertraline, and sertraline carries a lower risk of producing an adverse drug interaction than the other two. Rare side effects of SSRIs include angina due to vasospasm and prolongation of the prothrombin time. Escitalopram is the most specific of currently available SSRIs and appears to have no significant inhibitory effects on the P450 system. Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran block the reuptake of both norepinephrine and serotonin but produce relatively little in the way of traditional tricyclic side effects. Vortioxetine, also a 5-HT_{1A} agonist, and vilazodone block reuptake of serotonin but have negligible effects on norepinephrine reuptake, although vortioxetine may increase norepinephrine levels through wide effects on serotonergic receptors, as a 5-HT_{1A} agonist, 5-HT_{1B} partial agonist, and a 5-HT_{1D}, 5-HT₃, and 5-HT₇ antagonist. Unlike the SSRIs, venlafaxine and vortioxetine have relatively linear dose-response curves. Patients on immediate-release venlafaxine should be monitored for a possible increase in diastolic blood pressure, and multiple daily dosing is required because of the drug's short half-life. An extended-release form is available and has a somewhat lower incidence of gastrointestinal side effects. Mirtazapine is a tetracyclic that has a unique spectrum of activity, as it

increases nor adrenergic and serotonergic neurotransmission through a blockade of central α_2 -adrenergic receptors and postsynaptic 5-HT₂ and 5-HT₃ receptors. It is also strongly antihistaminic and, as such, may produce sedation. Levomilnacipran is the most noradrenergic of the SNRIs and theoretically may be appropriate for patients with more severe fatigue and anergia. Gepirone, an older drug recently approved, is a partial 5-HT_{1A} agonist and 5-HT_{2A} antagonist. With the exception of citalopram and escitalopram, each of the SSRIs may inhibit one or more cytochrome P450 enzymes. Depending on the specific isoenzyme involved, the metabolism of a number of concomitantly administered medications can be dramatically affected. Fluoxetine and paroxetine, for example, by inhibiting 2D6, can cause dramatic increases in the blood level of type 1C antiarrhythmics, whereas sertraline, by acting on 3A4, may alter blood levels of carbamazepine or digoxin. Depending on drug specificity for a particular CYP enzyme for its own metabolism, concomitant medications or dietary factors, such as grapefruit juice, may in turn affect the efficacy or toxicity of the SSRI. The MAOIs are highly effective, particularly in atypical depression, but the risk of hypertensive crisis following intake of tyramine-containing food or sympathomimetic drugs makes them inappropriate as first-line agents. Transdermal selegiline may avert this risk at low dose. Common side effects include orthostatic hypotension, weight gain, insomnia, and sexual dysfunction. MAOIs should not be used concomitantly with SSRIs, because of the risk of serotonin syndrome, or with TCAs, because of possible hyperadrenergic effects. Electroconvulsive therapy is at least as effective as medication, but its use is reserved for treatment-resistant cases and delusional depressions. rTMS is approved for treatment-resistant depression and has been shown to have efficacy in several controlled trials. Vagus nerve stimulation (VNS) has also recently been approved

for treatment-resistant depression, but its degree of efficacy is controversial. Some meta-analyses of low-intensity transcranial current stimulation (tCS) have shown a positive benefit over sham treatment, but whether this is comparable to or synergistic with antidepressant treatment is unclear. In off-label usage, intravenous ketamine, a dissociative anesthetic, and intranasal esketamine (an isomer that has FDA approval in treatment-resistant cases) have been shown to have short-term antidepressant efficacy, often after a single administration, and may decrease suicidality. Questions remain, however, about the risk/benefit ratio over the longer term. Psilocybin, a hallucinogen, has also shown some potential benefit in controlled administration. Lastly, deep brain stimulation of the ventral anterior limb of the internal capsule and of the subcallosal cingulate region has demonstrable efficacy in randomized experimental trials of treatment-resistant depression.

Postpartum depression may respond to any of the above interventions, but a neuroactive steroid, brexanolone (Zulresso), administered in a continuous intravenous infusion over 60 h, can provide symptomatic relief for at least 30 days. Sedation and loss of consciousness are possible adverse effects. An oral version, zuranolone (Zurzuvae), can be given on an outpatient basis. CHAPTER 463 Regardless of the treatment undertaken, the response should be evaluated after ~2 months. Three-quarters of patients show improvement by this time, but if remission is inadequate, the patient should be questioned about compliance, and an increase in medication dose should be considered if side effects are not troublesome. If this approach is unsuccessful, referral to a mental health specialist is advised. Strategies for treatment resistance include selection of an alternative drug, combinations of antidepressants, and/or adjunctive treatment with other classes of drugs, including lithium, thyroid hormone, L-methylfolate, S-adenosylmethionine, N-acetylcysteine,

atypical antipsychotic agents, and dopamine agonists. In switching to a different monotherapy, other drugs from the same class appear to be as likely to be efficacious as choosing a drug from a different class. A large randomized trial (STAR-D) was unable to show preferential efficacy, but the addition of certain atypical anti psychotic drugs (quetiapine extended-release; aripiprazole; brexpiprazole) has received FDA approval, as has usage of a combined medication, olanzapine and fluoxetine (Symbyax). Patients whose response to an SSRI wanes over time may benefit from the addition of buspirone (10 mg tid) or pindolol (2–5 mg tid) or small amounts of a TCA such as nortriptyline (25 mg bid or tid). Most patients will show some degree of response, but aggressive treatment should be pursued until remission is achieved, and drug treatment should be continued for at least 6–9 months to prevent relapse. In patients who have had two or more episodes of depression, indefinite maintenance treatment should be considered. Pharmacogenomic testing focusing on cytochrome p450 allelic variation may sometimes be helpful in identifying individuals who are poor or rapid metabolizers, but assessing pharmacodynamic gene variants has not been shown to be cost-effective or affect clinical outcomes. **Psychiatric Disorders** It is essential to educate patients both about depression and the benefits and side effects of medications they are receiving. Advice about stress reduction and cautions that alcohol may exacerbate depressive symptoms and impair drug response are helpful. Patients should be given time to describe their experience, their outlook, and the impact of the depression on them and their families. Occasional empathic silence may be as helpful for the treatment alliance as verbal reassurance. Controlled trials have shown that cognitivebehavioral and interpersonal therapies are effective in improving psychological and social adjustment and that a combined treatment approach is more successful than medication alone for many patients. ■ ■ **BIPOLAR DISORDER** Clinical Manifestations Bipolar disorder is characterized by unpredictable swings in mood from mania (or hypomania) to

depression. Some patients suffer only from recurrent attacks of mania, which in its pure form is associated with increased psychomotor activity; excessive social extroversion; decreased need for sleep; impulsivity and impaired judgment; and expansive, elated, grandiose, and some times irritable mood (Table 463-8). In severe mania, patients may experience delusions and paranoid thinking indistinguishable from schizophrenia. One-half of patients with bipolar disorder present not with euphoria but with a mixture of psychomotor agitation and activation, accompanied by dysphoria, anxiety, and irritability. It may be difficult to distinguish such a mixed state from agitated depression. In some bipolar patients (bipolar II disorder), the full criteria for mania are lacking, and the requisite recurrent depressions are separated by periods of mild activation and increased energy (hypomania). In cyclothymic disorder, there are numerous hypomanic periods, usually of relatively short duration, alternating with clusters of depressive symptoms that fail, either in severity or duration, to meet the criteria of major depression. The mood fluctuations are chronic and should be present for at least 2 years before the diagnosis is made.

PART 13 Neurologic Disorders Manic episodes typically emerge over a period of days to weeks, but onset within hours is possible, usually in the early-morning hours. An untreated episode of either depression or mania can be as short as several weeks or last as long as 8–12 months, and rare patients have an unremitting chronic course. The term rapid cycling is used for patients who have four or more episodes of either depression or mania in a given year. This pattern occurs in 15% of all patients, most of whom are women. In some cases, rapid cycling is linked to an underlying thyroid dysfunction, and in others, it is iatrogenically triggered by prolonged antidepressant treatment. Approximately one-half of patients have sustained difficulties in work performance and

psychosocial functioning, with depressive phases being more responsible for impairment than mania. Bipolar disorder is common, affecting ~1.5% of the population in the United States. Onset is typically between 20–30 years of age, but many individuals report premorbid symptoms in late childhood or early adolescence. The prevalence is similar for men and women; women are likely to have more depressive and men more manic episodes over a lifetime. Recognizing a bipolar diathesis in an individual who presents with a depressive episode but no history of mania is difficult but essential in optimizing treatment planning, because antidepressants may be contraindicated and result in symptom worsening and cycle acceleration. Suggestive features of bipolarity include a childhood onset, a history of antidepressant treatment failure, atypical features of hypomania and weight gain, and marked irritability or impulsivity.

Differential Diagnosis The differential diagnosis of mania includes secondary mania induced by stimulant or sympathomimetic drugs, hyperthyroidism, AIDS, neurologic disorders such as Huntington's or Wilson's disease, frontotemporal dementia, and cerebrovascular accidents. Comorbidity with alcohol and substance abuse is common, either because of shared genetic risk, poor judgment, and increased impulsivity or because of an attempt to self-treat the underlying mood symptoms and sleep disturbances.

Etiology and Pathophysiology Genetic predisposition to bipolar disorder is evident from family studies; the concordance rate for monozygotic twins approaches 80%. A number of risk genes that have been identified to date overlap with those conveying risk for other psychiatric disorders, such as schizophrenia and autism, implying some degree of shared pathophysiology. Replicated loci include the alpha subunit of the L-type calcium channel (CACNA1C), tenascin transmembrane protein 4 (ODZ4), ankyrin 3 (ANK3), neurocan (NCAN), and tetratricopeptide repeat and ankyrin repeat containing 1 (TRANK1). Common variants convey little individual risk but collectively account for 25% of heritability. A few rarer, more penetrant variants have also been reported, but no causative mutations have as yet been confirmed. Similarly, no clear biomarkers have been identified, but there is evidence for circadian rhythm and calcium dysregulation and oxidative stress, and mitochondrial, microRNA, and endoplasmic reticulum abnormalities. Reported MRI findings include gray matter thinning in frontal, temporal, and parietal cortex.

TREATMENT Bipolar Disorder (Table 463-9) Lithium carbonate is the mainstay of treatment in bipolar disorder, although paradoxically underutilized. Sodium valproate and carbamazepine, as well as a number of second-generation antipsychotic agents (e.g., aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, ziprasidone), also have FDA approval for the treatment of acute mania. Oxcarbazepine is not FDA approved but appears to enjoy carbamazepine's spectrum of efficacy. The response rate to lithium carbonate is 70–80% in acute mania, with beneficial effects appearing in 1–2 weeks. Lithium also has a prophylactic effect in prevention of recurrent mania and, to a lesser extent, in the prevention of recurrent depression, which is more difficult to treat than unipolar depression. A simple cation, lithium is rapidly absorbed from the gastrointestinal tract and remains unbound to plasma or tissue proteins. Some 95% of a given dose is excreted unchanged through the kidneys within 24 h. Serious side effects from lithium are rare, but minor complaints such as gastrointestinal discomfort, nausea, diarrhea, polyuria, weight gain, skin eruptions, alopecia, and edema are common. Over time, urine-concentrating ability may be decreased, but significant nephrotoxicity is relatively rare. Lithium exerts an antithyroid effect by interfering with the synthesis and release of thyroid hormones. More serious side effects include tremor, poor concentration and memory, ataxia, dysarthria, and incoordination. In the treatment of acute mania, lithium is initiated at 300 mg bid or tid, and the dose is then increased by 300 mg every 2–3 days to achieve blood levels of 0.8–1.2 meq/L. Because the therapeutic effect of lithium

may not appear until after 7–10 days of treatment, adjunctive usage of lorazepam (1–2 mg every 4 h) or clonazepam (0.5–1 mg every 4 h) may be beneficial to control agitation. Antipsychotics are indicated in patients with severe agitation who respond only partially to benzodiazepines. Patients using lithium should be monitored closely, because the blood levels required to achieve a therapeutic benefit are close to those associated with toxicity. Valproic acid may be more effective than lithium for patients who experience rapid cycling (i.e., more than four episodes a year) or who present with a mixed or dysphoric mania. Tremor and weight gain are the most common side effects; hepatotoxicity and pancreatitis are rare toxicities. The recurrent nature of bipolar mood disorder necessitates maintenance treatment. A sustained blood lithium level of at least 0.8 meq/L is important for optimal prophylaxis and has been shown to reduce the risk of suicide, a finding not yet apparent for other mood stabilizers. Decrease in acute suicidal risk may also result from treatment with parenteral ketamine or intranasal esketamine. Combinations of mood stabilizers together or with atypical antipsychotic drugs are sometimes required to maintain mood stability. Quetiapine extended release, olanzapine, risperidone, and lamotrigine have been approved for maintenance treatment as sole agents, in combination with lithium and with aripiprazole and ziprasidone as adjunctive drugs. Lurasidone, olanzapine/fluoxetine, and quetiapine are also approved to treat acute depressive episodes in bipolar disorder. Compliance is frequently an issue and often requires enlistment and education of concerned family members. Efforts to identify and modify psychosocial factors that may trigger episodes are important, as is an emphasis on lifestyle regularity (social rhythm therapy). Mobile apps for smartphones that alert the individual and clinician to changes in activity and speech are proving useful in early detection of behavioral change and in delivering clinical interventions and education. Antidepressant medications are sometimes required for the treatment of severe breakthrough depressions, but their use should generally be avoided during maintenance treatment because of the risk of precipitating mania or accelerating the cycle frequency. Alternative off-label agents for bipolar depression include pramipexole, modafinil, omega-3 fatty acids, and N-acetyl cysteine; interventions such as electroconvulsive

TABLE 463-8 Criteria for Bipolar I Disorder For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. **Manic Episode A.** A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary). **B.** During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity). 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). **C.** The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. **D.** The episode is not attributable to

the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition. Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis. Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Hypomanic Episode A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day. B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation. 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic. D. The disturbance in mood and the change in functioning are observable by others. E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic. F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition. Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis. Note: Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Major Depressive Episode A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.) 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think

or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying); recurrent suicidal ideation without a specific plan; a specific suicide plan; or a suicide attempt. B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. C. The episode is not attributable to the physiological effects of a substance or another medical condition. Note: Criteria A–C constitute a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss. Bipolar I Disorder A. Criteria have been met for at least one manic episode (Criteria A–D under "Manic Episode" above). B. At least one manic episode is not better explained by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder. Source: Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders-Text Revision, 5th ed. (Copyright © 2022). American Psychiatric Association. All Rights Reserved.

CHAPTER 463 Psychiatric Disorders

TABLE 463-9 Clinical Pharmacology of Mood Stabilizers AGENT AND DOSING SIDE EFFECTS AND OTHER EFFECTS Lithium Common Side Effects Starting dose: 300 mg bid or tid Therapeutic blood level: 0.8–1.2 meq/L Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism Blood level is increased by thiazides, tetracyclines, and NSAIDs Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors Rare side effects: Neurotoxicity, renal toxicity, hypercalcemia, ECG changes Valproic Acid Common Side Effects Starting dose: 250 mg tid Therapeutic blood level: 50–125 µg/mL Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia Inhibits hepatic metabolism of other medications PART 13 Neurologic Disorders Rare side effects: Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome Carbamazepine/ Oxcarbazepine Common Side Effects Starting dose: 200 mg bid for carbamazepine, 150 mg bid for oxcarbazepine Therapeutic blood level: 4–12 µg/mL for carbamazepine Nausea/anorexia, sedation, rash, dizziness/ ataxia Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications Rare side effects: Hyponatremia, agranulocytosis, Stevens-Johnson syndrome Lamotrigine Common Side Effects Starting dose: 25 mg/d Rash, dizziness, headache, tremor, sedation, nausea Rare side effect: Stevens-Johnson syndrome Abbreviations: ECG, electrocardiogram; NSAIDs, nonsteroidal anti-inflammatory drugs. therapy, light therapy, and rTMS may also be effective. Loss of efficacy over time may be observed with any of the mood-stabilizing agents. In such situations, an alternative agent or combination therapy is usually helpful. SOMATIC SYMPTOM DISORDER Many patients presenting in general medical practice, perhaps as many as 5–7%, will experience a somatic symptom(s) as particularly distressing and preoccupying, to the point that it comes to dominate their thoughts, feelings, and beliefs and interferes to a varying degree with everyday functioning. Although the absence of a

medical explanation for these complaints was historically emphasized as a diagnostic element, it has been recognized that the patient's interpretation and elaboration of the experience is the critical defining factor and that patients with well-established medical causation may qualify for the diagnosis. Multiple complaints are typical, but severe single symptoms can occur as well. Comorbidity with depressive and anxiety disorders is common and may affect the severity of the experience and its functional consequences. Personality factors may be a significant risk factor, as may a low level of educational or socioeconomic status or a history of recent stressful life events. Cultural factors are relevant as well and should be incorporated into the evaluation. Individuals who have persistent preoccupations about having or acquiring a serious illness, but who do not have a specific somatic complaint, may qualify for a related diagnosis—illness anxiety disorder. The diagnosis of conversion disorder (functional neurologic symptom disorder) is used to specifically identify individuals whose somatic complaints involve one or more symptoms of altered voluntary motor or sensory function that cannot be medically explained and that cause significant distress or impairment or require medical evaluation. In factitious illnesses, the patient consciously and voluntarily produces physical symptoms of illness. The term Munchausen's syndrome is reserved for individuals with particularly dramatic, chronic, or

severe factitious illness. In true factitious illness, the sick role itself is gratifying. A variety of signs, symptoms, and diseases have been either simulated or caused by factitious behavior, the most common including chronic diarrhea, fever of unknown origin, intestinal bleeding or hematuria, seizures, and hypoglycemia. Factitious disorder is usually not diagnosed until 5–10 years after its onset, and it can produce significant social and medical costs. In malingering, the fabrication derives from a desire for some external reward such as a narcotic medication or disability reimbursement.

TREATMENT Somatic Symptom Disorder and Related Disorders Patients with somatic symptom disorder are frequently subjected to many diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. Such an approach is doomed to failure and does not address the core issue. Successful treatment is best achieved through behavior modification, in which access to the physician is tightly regulated and adjusted to provide a sustained and predictable level of support that is less clearly contingent on the patient's level of presenting distress. Visits can be brief and should not be associated with a need for a diagnostic or treatment action. Although the literature is limited, some patients may benefit from antidepressant treatment. Any attempt to confront the patient usually creates a sense of humiliation and causes the patient to abandon treatment from that caregiver. A better strategy is to introduce psychological causation as one of a number of possible explanations in the differential diagnoses that are discussed. Without directly linking psychotherapeutic intervention to the diagnosis, the patient can be offered a face-saving means by which the pathologic relationship with the health care system can be examined and alternative approaches to life stressors developed. Specific medical treatments also may be indicated and effective in treating some of the functional consequences of conversion disorder.

FEEDING AND EATING DISORDERS ■ ■ CLINICAL MANIFESTATIONS

Feeding and eating disorders constitute a group of conditions in which there is a persistent disturbance of eating or associated behaviors that significantly impair an individual's physical health or psychosocial functioning. In DSM-5-TR, the described categories (with the exception of pica) are defined to be mutually exclusive in a given episode, based on the understanding that although they are phenotypically similar in some ways, they differ in course, prognosis, and effective treatment interventions. ■ ■ **PICA** Pica is diagnosed when the individual, aged >2 years, eats one or more nonnutritive, nonfood substances for a month or more and requires medical

attention as a result. There is usually no specific aversion to food in general but a preferential choice to ingest substances such as clay, starch, soap, paper, or ash. The diagnosis requires the exclusion of specific culturally approved practices and has not been commonly found to be caused by a specific nutritional deficiency. Onset is most common in childhood, but the disorder can occur in association with other major psychiatric conditions in adults. An association with pregnancy has been observed, but the condition is only diagnosed when medical risks are increased by the behavior. ■ ■ **RUMINATION DISORDER** In this condition, individuals who have no demonstrable associated gastrointestinal or other medical condition repeatedly regurgitate their food after eating and then either re chew or swallow it or spit it out. The behavior typically occurs on a daily basis and must persist for at least 1 month. Weight loss and malnutrition are common sequelae, and individuals may attempt to conceal their behavior, either by covering

their mouth or through social avoidance while eating. In infancy, the onset is typically between 3 and 12 months of age, and the behavior may remit spontaneously, although in some, it appears to be recurrent. ■ ■ **AVOIDANT/RESTRICTIVE FOOD INTAKE DISORDER** The cardinal feature of this disorder is avoidance or restriction of food intake, usually stemming from a lack of interest in or distaste of food and associated with weight loss, nutritional deficiency, dependency on nutritional supplementation, or marked impairment in psychosocial functioning, either alone or in combination. Culturally approved practices, such as fasting or a lack of available food, must be excluded as possible causes. The disorder is distinguished from anorexia nervosa by the presence of emotional factors, such as a fear of gaining weight and distortion of body image in the latter condition. Onset is usually in infancy or early childhood, but avoidant behaviors may persist into adulthood. The disorder is equally prevalent in males and females and is frequently comorbid with anxiety and cognitive and attention-deficit disorders and situations of familial stress.

Developmental delay and functional deficits may be significant if the disorder is long-standing and unrecognized. ■ ■ **ANOREXIA NERVOSA** Individuals are diagnosed with anorexia nervosa if they restrict their caloric intake to a degree that their body weight deviates significantly from age, gender, health, and developmental norms and if they also exhibit a fear of gaining weight and an associated disturbance in body image. The condition is further characterized by differentiating those who achieve their weight loss predominantly through restricting intake or by excessive exercise (restricting type) from those who engage in recurrent binge eating and/or subsequent purging, self-induced vomiting, and usage of enemas, laxatives, or diuretics (binge-eating/purging type). Such subtyping is more state- than trait-specific, as individuals may transition from one profile to the other over time. Determination of whether an individual satisfies the primary criterion of significant low weight is complex and must be individualized, using all available historical information and comparison of body habitus to international body-mass norms and guidelines. Individuals with anorexia nervosa frequently lack insight into their condition and are in denial about possible medical consequences; they often are not comforted by their achieved weight loss and persist in their behaviors despite having met previously self-designated weight goals. Alterations in the circuitry of reward sensitivity and executive function have been reported in anorexia, implicating disturbances in frontal cortex and anterior insula regulation of interoceptive awareness of satiety and hunger. Neurochemical findings, including the role of ghrelin, remain controversial. Onset is most common in adolescence, although onset in later life can occur. Many more females than males are affected, with a lifetime prevalence in women of up to 4%. The disorder appears most prevalent in postindustrialized and urbanized countries and is frequently comorbid with preexisting anxiety disorders. The medical consequences of prolonged anorexia nervosa are

multisystemic and can be life-threatening in severe presentations. Changes in laboratory values may be present, including leukopenia with lymphocytosis, elevations in blood urea nitrogen, and metabolic alkalosis and hypokalemia when purging is present. History and physical examination may reveal amenorrhea in females, skin abnormalities (petechiae, lanugo hair, dryness), and signs of hypometabolic function, including hypotension, hypothermia, and sinus bradycardia. Endocrine effects include hypogonadism, growth hormone resistance, and hypercor tisoemia. Osteoporosis is a longer-term concern. The course of the disorder is variable, with some individuals recovering after a single episode, while others exhibit recurrent episodes or a chronic course. Untreated anorexia has a mortality of 5.1/1000, the highest among psychiatric conditions. Maudsley Anorexia Nervosa Treatment for Adults (MANTRA) and eating disorder-focused cognitive-behavior therapy have proven to be effective therapies, with strict behavioral contingencies used when weight loss becomes critical. No pharmacologic intervention has proven to be specifically beneficial, but comorbid depression and anxiety should be treated. Weight gain

should be undertaken gradually with a goal of 0.5–1 pound per week to prevent refeeding syndrome. Most individuals are able to achieve remission within 5 years of the original diagnosis.

■ ■ **BULIMIA NERVOSA** Bulimia nervosa describes individuals who engage in recurrent and frequent (at least once a week for 3 months) periods of binge eating and who then resort to compensatory behaviors, such as self-induced purging, enemas, use of laxatives, or excessive exercise, to avoid weight gain. Binge eating itself is defined as excessive food intake in a prescribed period of time, usually <2 h. As in anorexia nervosa, disturbances in body image occur and promote the behavior, but unlike in anorexia, individuals are of normal weight or even somewhat overweight. Subjects typically describe a loss of control and express shame about their actions, and often relate that their episodes are triggered by feelings of negative self-esteem or social stresses. The lifetime prevalence in women is ~2%, with a 10:1 female-to-male ratio. The disorder typically begins in adolescence and may be persistent over a number of years. Transition to anorexia occurs in only 10–15% of cases. Many of the medical risks associated with bulimia nervosa parallel those of anorexia nervosa and are a direct consequence of purging, including fluid and electrolyte disturbances and cardiac conduction abnormalities. Physical examination often results in no specific findings, but dental erosion and parotid gland enlargement may be present. Effective treatment approaches include SSRI antidepressants, usually in combination with cognitive-behavioral, emotion regulation, or interpersonal-based psychotherapies. CHAPTER 463 Psychiatric Disorders ■

■ **BINGE-EATING DISORDER** Binge-eating disorder is distinguished from bulimia nervosa by the absence of compensatory behaviors to prevent weight gain after an episode and by a lack of effort to restrict weight gain between episodes. Other features are similar, including distress over the behavior and the experience of loss of control, resulting in eating more rapidly or in greater amounts than intended or eating when not hungry. The 12-month prevalence in females is 1.6%, with a much lower female-to-male ratio than bulimia nervosa. Little is known about the course of the disorder, given its recent categorization, but its prognosis is markedly better than for other eating disorders, both in terms of its natural course and response to treatment. Transition to other eating disorder conditions is thought to be rare. PERSONALITY DISORDERS ■ ■ **CLINICAL MANIFESTATIONS** Personality disorders are characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. The observed behaviors are not secondary to another mental disorder, nor are they precipitated by substance abuse or a general medical condition. This

distinction is often difficult to make in clinical practice, because personality change may be the first sign of serious neurologic, endocrine, or other medical illness. Patients with frontal-lobe tumors, for example, can present with changes in motivation and personality while the results of the neurologic examination remain within normal limits. Individuals with personality disorders are often regarded as “difficult patients” in clinical medical practice because they are seen as excessively demanding and/or unwilling to follow recommended treatment plans. Although DSM-5-TR portrays personality disorders as qualitatively distinct categories, there is an alternative and emerging perspective that personality characteristics vary as a continuum between normal functioning and formal mental disorder, the essential features being moderate or greater impairment in self/interpersonal functioning and one or more pathological personality traits. Personality disorders have been grouped into three overlapping clusters. Cluster A includes paranoid, schizoid, and schizotypal personality disorders. It includes individuals who are odd and eccentric and who maintain an emotional distance from others. Individuals have a restricted emotional range and remain socially isolated. Patients with schizotypal personality disorder frequently have unusual perceptual

experiences and express magical beliefs about the external world. The essential feature of paranoid personality disorder is a pervasive mistrust and suspiciousness of others to an extent that is unjustified by available evidence. Cluster B disorders include antisocial, borderline, histrionic, and narcissistic types and describe individuals whose behavior is impulsive, excessively emotional, and erratic. Cluster C incorporates avoidant, dependent, and obsessive-compulsive personality types; enduring traits are anxiety and fear. The boundaries between cluster types are to some extent artificial, and many patients who meet criteria for one personality disorder also meet criteria for aspects of another. The risk of a comorbid major mental disorder is increased in patients who qualify for a diagnosis of personality disorder.

■ ■ **ETIOLOGY AND PATHOPHYSIOLOGY** Genetic studies have increasingly suggested a genetic contribution to the development of personality disorders. One study of 106,000 subjects identified nine loci significantly linked to aspects of neuroticism.

PART 13 Neurologic Disorders TREATMENT

Personality Disorders Dialectical behavior therapy (DBT) is a cognitive-behavioral approach that focuses on behavioral change while providing acceptance, compassion, and validation of the patient. Several randomized trials have demonstrated the efficacy of DBT in the treatment of personality disorders. Antidepressant medications and low-dose antipsychotic drugs have some efficacy in cluster A personality disorders, whereas anticonvulsant mood-stabilizing agents and MAOIs may be considered for patients with cluster B diagnoses who show marked mood reactivity, behavioral dyscontrol, and/or rejection hypersensitivity. Anxious or fearful cluster C patients often respond to medications used for axis I anxiety disorders (see above). It is important that the physician and the patient have reasonable expectations vis-à-vis the possible benefit of any medication used and its side effects. Improvement may be subtle and observable only over time.

SCHIZOPHRENIA ■ ■ **CLINICAL MANIFESTATIONS** Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. There are no pathognomonic features. The syndrome commonly begins in late adolescence, has an insidious (and less commonly, acute) onset, and, often, a poor outcome, progressing from social withdrawal and perceptual distortions to recurrent delusions and hallucinations. Patients may present with positive symptoms (such as conceptual disorganization, delusions, or hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired

concentration, and diminished social engagement) and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. Disorganized thinking or speech and grossly disorganized motor behavior, including catatonia, may also be present. As individuals age, positive psychotic symptoms tend to attenuate, and some measure of social and occupational function may be regained. “Negative” symptoms predominate in one-third of the schizophrenic population and are associated with a poor longterm outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical. The term schizophreniform disorder describes patients who meet the symptom requirements but not the duration requirements for schizophrenia, and schizoaffective disorder is used for those who manifest symptoms of schizophrenia and independent periods of mood disturbance. The terms schizotypal and schizoid refer to specific personality disorders and are discussed in that section. The diagnosis of delusional disorder is used for individuals who have delusions of various content for at least 1 month but who otherwise do not meet criteria for schizophrenia. Patients who experience a sudden onset of a brief (<1 month) alteration in thought processing, characterized

by delusions, hallucinations, disorganized speech, or gross motor behavior, are most appropriately designated as having a brief psychotic disorder. Catatonia is recognized as a nonspecific syndrome that can occur as a consequence of other severe psychiatric/medical disorders and is diagnosed by the documentation of three or more of a cluster of motor and behavioral symptoms, including stupor, cataplexy, mutism, waxy flexibility, and stereotypy, among others. Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic patients commit suicide. Schizophrenia is present in 0.85% of individuals worldwide, with a lifetime prevalence of ~1–1.5%. An estimated 300,000 episodes of acute schizophrenia occur annually in the United States, resulting in direct and indirect costs of \$155.7 billion. ■ ■DIFFERENTIAL DIAGNOSIS The diagnosis is principally one of exclusion, requiring the absence of significant associated mood symptoms, any relevant medical condition, and substance abuse. Drug reactions that cause hallucinations, paranoia, confusion, or bizarre behavior may be dose-related or idiosyncratic; parkinsonian medications, clonidine, quinacrine, and procaine derivatives are the most common prescription medications associated with these symptoms. Drug causes should be ruled out in any case of newly emergent psychosis. The general neurologic examination in patients with schizophrenia is usually normal, but motor rigidity, tremor, and dyskinesias are noted in one-quarter of untreated patients. ■ ■EPIDEMIOLOGY AND PATHOPHYSIOLOGY Epidemiologic surveys identify several risk factors for schizophrenia, including genetic susceptibility, early developmental insults, winter birth, and increasing parental age. Genetic factors are involved in at least a subset of individuals who develop schizophrenia. Schizophrenia is observed in ~6.6% of all first-degree relatives of an affected proband. If both parents are affected, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50%, compared to 10% for dizygotic twins. Schizophrenia-prone families are also at risk for other psychiatric disorders, including schizoaffective disorder and schizotypal and schizoid personality disorders, the latter terms designating individuals who show a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions. Large-scale GWASs have identified several hundred small effect risk loci and a few larger effect copy number variants, along with epigenetic effects, and have led to initial exploration in the clinical use of polygenic risk scores in diagnosis and prognosis. Pathways identified include ones involved in immunity, inflammation,

and cell signaling. There is also recent evidence that brain gene expression in schizophrenia is similar to that seen in older aging adults without the disorder, implicating parallel mechanisms for cognitive deterioration. **TREATMENT** Schizophrenia Antipsychotic agents (Table 463-10) are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions, and thought disorders, regardless of etiology. The mechanism of action involves, at least in part, binding to dopamine D2/D3 receptors in the ventral striatum; the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D2 receptor, and even the newer “atypical” agents exert some degree of D2 receptor blockade. All current neuroleptics induce expression of the immediate-early gene c-fos in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The development of newer atypical neuroleptics, however, is increasingly focusing on different targets: D3, 5-HT1A, 5-HT7, mGlu2/3, and muscarinic acetylcholine (M1, M4) receptors; α 1- and α 2-noradrenergic activity; and altering the relationship between 5-HT2 and D2 receptor activity, resulting in faster dissociation of D2 binding and effects on neuroplasticity.

TABLE 463-10 Antipsychotic Agents USUAL PO DAILY DOSE (mg) SIDE EFFECTS SEDATION

COMMENTS	NAME	First-Generation Antipsychotics	Low potency	Chlorpromazine (Thorazine)
Thioridazine (Mellaril)	100–1000	100–600	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	Midpotency
			Trifluoperazine (Stelazine)	2–50 Fewer anticholinergic side effects ++ Well tolerated by most patients
			Perphenazine (Trilafon)	4–64 Fewer EPSEs than with higher-potency agents ++
			Loxapine (Loxitane)	30–100 Frequent EPSEs ++
			Molindone (Moban)	30–100 Frequent EPSEs

Little weight gain	High potency	Haloperidol (Haldol)	5–20	No anticholinergic side effects; EPSEs often prominent
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	Thiothixene (Navane)
2–50	Frequent EPSEs	0/+	Second-Generation Antipsychotics	Clozapine (Clozaril)
150–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	Risperidone (Risperdal)	2–8	Orthostasis + Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain ++ Mild prolactin elevation	Quetiapine (Seroquel)	350–800
Sedation; weight gain; anxiety +++	bid dosing	Ziprasidone (Geodon)	120–200	Orthostatic hypotension +/+ + Minimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist; extended-release available
Paliperidone (Invega)	3–12	Restlessness, EPSEs, increased prolactin, headache +	Active metabolite of risperidone	Iloperidone (Fanapt)
12–24	Dizziness, hypotension	0/+	Requires dose titration; long-acting injectable available	Asenapine (Saphris)
10–20	Dizziness, anxiety, EPSEs, minimal weight gain ++	Sublingual tablets; bid dosing	Lurasidone (Latuda)	40–80
Nausea, EPSEs ++	Uses CYP3A4	Brexipiprazole (Rexulti)	1–4	Anxiety, dizziness, fatigue ++
CYP3A4 and 2D6 interactions	Pimavanserin (Nuplazid)			

Edema, confusion, sedation ++ Approved for Parkinson’s disease psychosis Cariprazine (Vraylar)
Lumateperone (Caplyta) 1.5–6

EPSEs, vomiting Fatigue, dry mouth; no apparent metabolic/motor effects Abbreviations: EPSEs, extrapyramidal side effects; WBC, white blood cell. Conventional neuroleptics differ in their potency and side effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, whereas higher-potency antipsychotics, such as haloperidol, perphenazine, and thiothixene, are more likely to induce

extrapyramidal side effects. The model “atypical” antipsychotic agent is clozapine, a dibenzodiazepine that has a greater potency in blocking the 5-HT₂ than the D₂ receptor and a much higher affinity for the D₄ than the D₂ receptor. Its principal disadvantage is a risk of blood dyscrasias. Paliperidone is a metabolite of risperidone and shares many of its properties. Unlike other antipsychotics, clozapine does not cause a rise in prolactin levels. Approximately 30% of patients who do not benefit from conventional antipsychotic agents will have a better response to this drug, which also has a demonstrated superiority to other antipsychotic agents in preventing suicide; however, its side effect profile makes it most appropriate for treatment-resistant cases. Risperidone, a benzisoxazole derivative, is more potent at 5-HT₂ than D₂ receptor sites, like clozapine, but it also exerts significant α_2 antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasias. Olanzapine is similar neurochemically to clozapine but has a significant risk of inducing weight gain. Quetiapine is distinct in having a

+++ EPSEs usually not prominent; can cause anticholinergic delirium in elderly patients 0/+ Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available CHAPTER 463 Psychiatric Disorders

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Requires weekly WBC count for first 6 months, then biweekly if stable ++ ++ Preferential D₃ receptor affinity 5-HT_A > D₂ receptor affinity weak D₂ effect but potent α_1 and histamine blockade. Ziprasidone causes minimal weight gain and is unlikely to increase prolactin but may increase QT prolongation. Aripiprazole also has little risk of weight gain or prolactin increase but may increase anxiety, nausea, and insomnia as a result of its partial agonist properties. Asenapine is associated with minimal weight gain and anticholinergic effect but may have a higher than expected risk of extrapyramidal symptoms (EPSs). Cariprazine, a D₂/D₃ partial agonist, has no QT or prolactin elevation risk but can result in EPS as well. Antipsychotic agents are effective in 70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6–8 weeks. The choice of agent depends principally on the side effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. An equivalent treatment response can usually be achieved with relatively low doses of any drug selected (i.e., 4–6 mg/d of haloperidol, 10–15 mg of olanzapine, or 4–6 mg/d of risperidone). Doses in this range result in >80% D₂ receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent

drug treatment is less effective than regular dosing, but gradual dose reduction is likely to improve social functioning in many schizophrenic patients who have been maintained at high doses.

If medications are completely discontinued, however, the relapse rate is 60% within 6 months. Long-acting injectable (LAI) preparations (risperidone, paliperidone, olanzapine, aripiprazole) are considered when noncompliance with oral therapy leads to relapses but should not be considered interchangeable because the agents differ in their indications, injection intervals and sites/volumes,

and possible adverse reactions, among other factors. Extended treatment studies indicate a significant decrease in relapse with LAI usage. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with first-generation agents and may contribute to poor adherence if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexy phenidyl, 2 mg bid, or benztropine mesylate, 1–2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge, including hyperprolactinemia, ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). The most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment. PART 13 Neurologic Disorders The risk of type 2 diabetes mellitus appears to be increased in schizophrenia, and second-generation agents as a group, with the exception of lurasidone, produce greater adverse effects on glucose regulation, independent of effects on obesity, than traditional agents. Clozapine, olanzapine, and quetiapine seem more likely to cause hyperglycemia, weight gain, and hypertriglyceridemia than other atypical antipsychotic drugs. Close monitoring of plasma glucose and lipid levels is indicated with the use of these agents. A serious side effect of long-term use of first-generation and, to a lesser extent, second-generation antipsychotic agents is tardive dyskinesia, characterized by repetitive, involuntary, and potentially irreversible movements of the tongue and lips (buccolingual-masticatory triad) and, in approximately half of cases, choreoathetosis. Tardive dyskinesia has an incidence of 2–4% per year of exposure and a prevalence of 20% in chronically treated patients. The prevalence increases with age, total dose, and duration of drug administration and may involve formation of free radicals and perhaps mitochondrial energy failure. Valbenazine (Ingrezza), a vesicular monoamine transporter 2 inhibitor that depletes pre synaptic dopamine, is approved for treatment of tardive dyskinesia. The CATIE study, a large-scale investigation of the effectiveness of antipsychotic agents in “real-world” patients, revealed a high rate of discontinuation of treatment after >18 months. Olanzapine showed greater effectiveness than quetiapine, risperidone, perphenazine, or ziprasidone but also a higher discontinuation rate due to weight gain and metabolic effects. Surprisingly, perphenazine, a first-generation agent, showed little evidence of inferiority to newer drugs. Drug treatment of schizophrenia is by itself insufficient. Educational efforts directed toward families and relevant community resources have proved to be necessary to maintain stability and optimize outcome. A collaborative treatment model using social cognition interventions and involving a multidisciplinary casemanagement team that seeks out and closely follows the patient in the community has proved particularly effective. Attempts to prevent schizophrenia through early identification and treatment (both psychosocial and psychopharmacologic) of high-risk children and adolescents are currently being evaluated.

ASSESSMENT AND EVALUATION OF VIOLENCE Primary care physicians may encounter situations in which family, domestic, or societal violence is discovered or suspected. Such an awareness can carry legal and moral obligations; many state laws mandate reporting of child, spousal, and elder

abuse. Physicians are frequently the first point of contact for both victim and abuser. Approximately 2 million older Americans and 1.5 million U.S. children are thought to experience some form of physical maltreatment each year. Spousal abuse is believed to be even more prevalent. An interview study of 24,000 women in 10 countries found a lifetime prevalence of physical or sexual violence that ranged from 15–71%; these individuals are more likely to suffer from depression, anxiety, and substance abuse and to have attempted suicide. In addition, abused individuals frequently express low self-esteem, vague somatic symptomatology, social isolation, and a passive feeling of loss of control. Although it is essential to treat these elements in the victim, the first obligation is to ensure that the perpetrator has taken responsibility for preventing any further violence. Substance abuse and/or dependence and serious mental illness in the abuser may contribute to the risk of harm and require direct intervention. Depending on the situation, law enforcement agencies, community resources such as support groups and shelters, and individual and family counseling can be appropriate components of a treatment plan. A safety plan should be formulated with the victim, in addition to providing information about abuse, its likelihood of recurrence, and its tendency to increase in severity and frequency. Antianxiety and antidepressant medications may sometimes be useful in treating the acute symptoms, but only if independent evidence for an appropriate psychiatric diagnosis exists. ■ ■ FURTHER READING Alon N et al: Social determinants of mental health in major depressive disorder: Umbrella review of 26 meta-analyses and systemic reviews. *Psychiatry Res* 335:115854, 2024. Anderson E et al: Depression treatment options and managing depression in primary care. *N Eng J Med* 390:e44, 2024. Barry R et al: Prevalence of mental health disorders among individuals experiencing homelessness: A systematic review and meta-analysis. *JAMA Psychiatry* 81:691, 2024. Bertolini F et al: Early pharmacological interventions for prevention of post-traumatic stress disorder (PTSD) in individuals experiencing acute traumatic stress symptoms. *Cochrane Database Sys Rev* 5:CD013613, 2024. Birnbaum R, Weinberger DR: The genesis of schizophrenia: An origin story. *Am J Psychiatry* 181:482, 2024. Borque VR et al: Genetic and phenotypic similarities across major psychiatric disorders: A systematic review and quantitative assessment. *Trans Psychiatry* 14:171, 2024. Cristancho M et al: Depression-advanced treatments for treatment resistant depression. *N Eng J Med* 390:e44, 2024. Gargano SP et al: A closer look to neural pathways and psychopharmacology of obsessive compulsive disorder. *Front Behav Neurosci* 17:1282246, 2023. Guaiana G et al: Pharmacological treatment in panic disorder in adults: A network meta-analysis. *Cochrane Database Sys Rev* 11:1465,

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