# 14 - 9 Anxiety Disorders

# 01 - 9.1 Overview

# 9.1 Overview

Anxiety Disorders 9.1 Overview Anxiety represents a core phenomenon around which considerable psychiatric theory has been organized. Thus, the term “anxiety” has played a central role in psychodynamic theory, as well as in neuroscience-focused research and various schools of thought heavily influenced by cognitive-behavioral principles. Anxiety disorders are associated with significant morbidity and often are chronic and resistant to treatment. Anxiety disorders can be viewed as a family of related but distinct mental disorders, which include (1) panic disorder, (2) agoraphobia, (3) specific phobia, (4) social anxiety disorder or phobia, and (5) generalized anxiety disorder. Each of these disorders is discussed in detail in the sections that follow. A fascinating aspect of anxiety disorders is the exquisite interplay of genetic and experiential factors. Little doubt exists that abnormal genes predispose to pathological anxiety states; however, evidence clearly indicates that traumatic life events and stress are also etiologically important. Thus, the study of anxiety disorders presents a unique opportunity to understand the relation between nature and nurture in the etiology of mental disorders. NORMAL ANXIETY Everyone experiences anxiety. It is characterized most commonly as a diffuse, unpleasant, vague sense of apprehension, often accompanied by autonomic symptoms such as headache, perspiration, palpitations, tightness in the chest, mild stomach discomfort, and restlessness, indicated by an inability to sit or stand still for long. The particular constellation of symptoms present during anxiety tends to vary among persons (Table 9.1-1). Table 9.1-1 Peripheral Manifestations of Anxiety

Fear versus Anxiety Anxiety is an alerting signal; it warns of impending danger and enables a person to take measures to deal with a threat. Fear is a similar alerting signal, but it should be differentiated from anxiety. Fear is a response to a known, external, definite, or nonconflictual threat; anxiety is a response to a threat that is unknown, internal, vague, or conflictual. This distinction between fear and anxiety arose accidentally. When Freud’s early translator mistranslated angst, the German word for “fear,” as anxiety, Freud himself generally ignored the distinction that associates anxiety with a repressed, unconscious object and fear with a known, external object. The distinction may be difficult to make because fear can also be caused by an unconscious, repressed, internal object displaced to another object in the external world. For example, a boy may fear barking dogs because he actually fears his father and unconsciously associates his father with barking dogs. Nevertheless, according to postfreudian psychoanalytic formulations, the separation of fear and anxiety is psychologically justifiable. The emotion caused by a rapidly approaching car as a person crosses the street differs from the vague discomfort a person may experience when meeting new persons in a strange setting. The main psychological difference between the two emotional responses is the suddenness of fear and the insidiousness of anxiety. In 1896, Charles Darwin gave the following psychophysiological description of acute fear merging into terror: Fear is often preceded by astonishment, and is so far akin to it, that both lead

to the senses of sight and learning being instantly aroused. In both cases the eyes and mouth are widely opened, and the eyebrows raised. The frightened man at first stands like a statue motionless and breathless, or crouches down as if instinctively to escape observation. The heart beats quickly and violently, so that it palpitates or knocks

against the ribs; but it is very doubtful whether it then works more efficiently than usual, so as to send a greater supply of blood to all parts of the body; for the skin instantly becomes pale, as during incipient faintness. This paleness of the surface, however, is probably in large part, or exclusively, due to the vasomotor center being affected in such a manner as to cause the contraction of the small arteries of the skin. That the skin is much affected under the sense of great fear, we see in the marvelous and inexplicable manner in which perspiration immediately exudes from it. This exudation is all the more remarkable, as the surface is then cold, and hence the term a cold sweat; whereas, the sudorific glands are properly excited into action when the surface is heated. The hairs also on the skin stand erect; and the superficial muscles shiver. In connection with the disturbed action of the heart, the breathing is hurried. The salivary glands act imperfectly; the mouth becomes dry, and is often opened and shut. I have also noticed that under slight fear there is a strong tendency to yawn. One of the best-marked symptoms is the trembling of all the muscles of the body; and this is often first seen in the lips. From this cause, and from the dryness of the mouth, the voice becomes husky or indistinct, or may altogether fail.... As fear increases into an agony of terror, we behold, as under all violent emotions, diversified results. The heart beats wildly or may fail to act and faintness ensues; there is a deathlike pallor; the breathing is labored; the wings of the nostrils are widely dilated; there is a gasping and convulsive motion on the lips, a tremor on the hollow cheek, a gulping and catching of the throat; the uncovered and protruding eyeballs are fixed on the object of terror; or they may roll restlessly from side to side. The pupils are said to be enormously dilated. All the muscles of the body may become rigid, or may be thrown into convulsive movements. The hands are alternately clenched and opened, often with a twitching movement. The arms may be protruded, as if to avert some dreadful danger, or may be thrown wildly over the head....In other cases there is a sudden and uncontrollable tendency to headlong flight; and so strong is this, that the boldest soldiers may be seized with a sudden panic. Is Anxiety Adaptive? Anxiety and fear both are alerting signals and act as a warning of an internal and external threat. Anxiety can be conceptualized as a normal and adaptive response that has lifesaving qualities and warns of threats of bodily damage, pain, helplessness, possible punishment, or the frustration of social or bodily needs; of separation from loved ones; of a menace to one’s success or status; and ultimately of threats to unity or wholeness. It prompts a person to take the necessary steps to prevent the threat or to lessen its consequences. This preparation is accompanied by increased somatic and autonomic activity controlled by the interaction of the sympathetic and parasympathetic nervous systems. Examples of a person warding off threats in daily life include getting down to the hard work of preparing for an examination, dodging a ball thrown at the head, sneaking into the dormitory after curfew to prevent punishment, and running to

catch the last commuter train. Thus, anxiety prevents damage by alerting the person to carry out certain acts that forestall the danger. Stress and Anxiety Whether an event is perceived as stressful depends on the nature of the event and on the person’s resources, psychological defenses, and coping mechanisms. All involve the ego, a collective abstraction for the process by which a person perceives, thinks, and acts on external events or internal drives. A person whose

ego is functioning properly is in adaptive balance with both external and internal worlds; if the ego is not functioning properly and the resulting imbalance continues sufficiently long, the person experiences chronic anxiety. Whether the imbalance is external, between the pressures of the outside world and the person's ego, or internal, between the person's impulses (e.g., aggressive, sexual, and dependent impulses) and conscience, the imbalance produces a conflict. Whereas externally caused conflicts are usually interpersonal, those that are internally caused are intrapsychic or intrapersonal. A combination of the two is possible, as in the case of employees whose excessively demanding and critical boss provokes impulses that they must control for fear of losing their jobs. Interpersonal and intrapsychic conflicts, in fact, are usually intertwined. Because human beings are social, their main conflicts are usually with other persons. Symptoms of Anxiety The experience of anxiety has two components: the awareness of the physiological sensations (e.g., palpitations and sweating) and the awareness of being nervous or frightened. A feeling of shame may increase anxiety—"Others will recognize that I am frightened." Many persons are astonished to find out that others are not aware of their anxiety or, if they are, do not appreciate its intensity. In addition to motor and visceral effects, anxiety affects thinking, perception, and learning. It tends to produce confusion and distortions of perception, not only of time and space but also of persons and the meanings of events. These distortions can interfere with learning by lowering concentration, reducing recall, and impairing the ability to relate one item to another—that is, to make associations. An important aspect of emotions is their effect on the selectivity of attention. Anxious persons likely select certain things in their environment and overlook others in their effort to prove that they are justified in considering the situation frightening. If they falsely justify their fear, they augment their anxieties by the selective response and set up a vicious circle of anxiety, distorted perception, and increased anxiety. If, alternatively, they falsely reassure themselves by selective thinking, appropriate anxiety may be reduced, and they may fail to take necessary precautions. PATHOLOGICAL ANXIETY

Epidemiology The anxiety disorders make up one of the most common groups of psychiatric disorders. The National Comorbidity Study reported that one of four persons met the diagnostic criteria for at least one anxiety disorder and that there is a 12-month prevalence rate of 17.7 percent. Women (30.5 percent lifetime prevalence) are more likely to have an anxiety disorder than are men (19.2 percent lifetime prevalence). The prevalence of anxiety disorders decreases with higher socioeconomic status. Contributions of Psychological Sciences Three major schools of psychological theory—psychoanalytic, behavioral, and existential—have contributed theories about the causes of anxiety. Each theory has both conceptual and practical usefulness in treating anxiety disorders. Psychoanalytic Theories. Although Freud originally believed that anxiety stemmed from a physiological buildup of libido, he ultimately redefined anxiety as a signal of the presence of danger in the unconscious. Anxiety was viewed as the result of psychic conflict between unconscious sexual or aggressive wishes and corresponding threats from the superego or external reality. In response to this signal, the ego mobilized defense mechanisms to prevent unacceptable thoughts and feelings from emerging into conscious awareness. In his classic paper "Inhibitions, Symptoms, and Anxiety," Freud states that "it was anxiety which produced repression and not, as I formerly believed, repression which produced anxiety." Today, many neurobiologists continue to substantiate many of Freud's original ideas and theories. One example is the role of the amygdala, which subserves the fear response without any reference to conscious memory and substantiates Freud's concept of an unconscious memory system for anxiety responses. One of the unfortunate consequences of regarding the symptom of anxiety as a disorder rather than a signal is that the

underlying sources of the anxiety may be ignored. From a psychodynamic perspective, the goal of therapy is not necessary to eliminate all anxiety but to increase anxiety tolerance—that is, the capacity to experience anxiety—and use it as a signal to investigate the underlying conflict that has created it. Anxiety appears in response to various situations during the life cycle, and although psychopharmacological agents may ameliorate symptoms, they may do nothing to address the life situation or its internal correlates that have induced the state of anxiety. In the following case, a disturbing fantasy precipitated an anxiety attack. A married man 32 years of age was referred for therapy for severe and incapacitating anxiety, which was clinically manifested as repeated outbreaks of acute attacks of panic. Initially, he had absolutely no idea what had precipitated his attacks, nor were they associated with any conscious mental content. In the early weeks of treatment, he spent most of his time trying to impress the doctor with how

hard he had worked and how effectively he had functioned before he was taken ill. At the same time, he described how fearful he was that he would fail at a new business venture he had embarked on. One day, with obvious acute anxiety that practically prevented him from talking, he revealed a fantasy that had suddenly popped into his mind a day or two before and had led to the outbreak of a severe anxiety attack. He had had the image of a large spike being driven through his penis. He also recalled that, as a child of 7, he was fascinated by his mother’s clothing and that, on occasion, when she was out of the house, he dressed himself up in them. As an adult, he was fascinated by female lingerie and would sometimes find himself impelled by a desire to wear women’s clothing. He had never yielded to the impulse, but on those occasions when the idea entered his consciousness, he became overwhelmed by acute anxiety and panic. To understand fully a particular patient’s anxiety from a psychodynamic view, it is often useful to relate the anxiety to developmental issues. At the earliest level, disintegration anxiety may be present. This anxiety derives from the fear that the self will fragment because others are not responding with needed affirmation and validation. Persecutory anxiety can be connected with the perception that the self is being invaded and annihilated by an outside malevolent force. Another source of anxiety involves a child who fears losing the love or approval of a parent or loved object. Freud’s theory of castration anxiety is linked to the oedipal phase of development in boys, in which a powerful parental figure, usually the father, may damage the little boy’s genitals or otherwise cause bodily harm. At the most mature level, superego anxiety is related to guilt feelings about not living up to internalized standards of moral behavior derived from the parents. Often, a psychodynamic interview can elucidate the principal level of anxiety with which a patient is dealing. Some anxiety is obviously related to multiple conflicts at various developmental levels. Behavioral Theories. The behavioral or learning theories of anxiety postulate that anxiety is a conditioned response to a specific environmental stimulus. In a model of classic conditioning, a girl raised by an abusive father, for example, may become anxious as soon as she sees the abusive father. Through generalization, she may come to distrust all men. In the social learning model, a child may develop an anxiety response by imitating the anxiety in the environment, such as in anxious parents. Existential Theories. Existential theories of anxiety provide models for generalized anxiety, in which no specifically identifiable stimulus exists for a chronically anxious feeling. The central concept of existential theory is that persons experience feelings of living in a purposeless universe. Anxiety is their response to the perceived void in existence and meaning. Such existential concerns may have increased since the development of nuclear weapons and bioterrorism.

Contributions of Biological Sciences Autonomic Nervous System. Stimulation of the autonomic nervous system causes certain symptoms—cardiovascular (e.g., tachycardia), muscular (e.g., headache), gastrointestinal (e.g., diarrhea), and respiratory (e.g., tachypnea). The autonomic nervous systems of some patients with anxiety disorder, especially those with panic disorder, exhibit increased sympathetic tone, adapt slowly to repeated stimuli, and respond excessively to moderate stimuli. Neurotransmitters. The three major neurotransmitters associated with anxiety on the bases of animal studies and responses to drug treatment are norepinephrine (NE), serotonin, and γ-aminobutyric acid (GABA). Much of the basic neuroscience information about anxiety comes from animal experiments involving behavioral paradigms and psychoactive agents. One such experiment to study anxiety was the conflict test, in which the animal is simultaneously presented with stimuli that are positive (e.g., food) and negative (e.g., electric shock). Anxiolytic drugs (e.g., benzodiazepines) tend to facilitate the adaptation of the animal to this situation, but other drugs (e.g., amphetamines) further disrupt the animal's behavioral responses. NOREPINEPHRINE. Chronic symptoms experienced by patients with anxiety disorder, such as panic attacks, insomnia, startle, and autonomic hyperarousal, are characteristic of increased noradrenergic function. The general theory about the role of norepinephrine in anxiety disorders is that affected patients may have a poorly regulated noradrenergic system with occasional bursts of activity. The cell bodies of the noradrenergic system are primarily localized to the locus ceruleus in the rostral pons, and they project their axons to the cerebral cortex, the limbic system, the brainstem, and the spinal cord. Experiments in primates have demonstrated that stimulation of the locus ceruleus produces a fear response in the animals and that ablation of the same area inhibits or completely blocks the ability of the animals to form a fear response. Human studies have found that in patients with panic disorder, β-adrenergic receptor agonists (e.g., isoproterenol [Isuprel]) and α2-adrenergic receptor antagonists (e.g., yohimbine [Yocon]) can provoke frequent and severe panic attacks. Conversely, clonidine (Catapres), an α2-receptor agonist, reduces anxiety symptoms in some experimental and therapeutic situations. A less consistent finding is that patients with anxiety disorders, particularly panic disorder, have elevated cerebrospinal fluid (CSF) or urinary levels of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG). HYPOTHALAMIC–PITUITARY–ADRENAL AXIS. Consistent evidence indicates that many forms of psychological stress increase the synthesis and release of cortisol. Cortisol serves to mobilize and to replenish energy stores and contributes to increased arousal, vigilance, focused attention, and memory formation; inhibition of the growth and reproductive system; and containment of the immune response. Excessive and sustained cortisol

secretion can have serious adverse effects, including hypertension, osteoporosis, immunosuppression, insulin resistance, dyslipidemia, dyscoagulation, and, ultimately, atherosclerosis and cardiovascular disease. Alterations in hypothalamic–pituitary– adrenal (HPA) axis function have been demonstrated in PTSD. In patients with panic disorder, blunted adrenocorticoid hormone (ACTH) responses to corticotropin-releasing factor (CRF) have been reported in some studies and not in others. CORTICOTROPIN-RELEASING HORMONE (CRH). One of the most important mediators of the stress response, CRH coordinates the adaptive behavioral and physiological changes that occur during stress. Hypothalamic levels of CRH are increased by stress, resulting in activation of the HPA axis and increased release of cortisol and dehydroepiandrosterone (DHEA). CRH also inhibits a variety of neurovegetative functions, such as food intake, sexual activity, and endocrine programs for growth and reproduction. SEROTONIN. The identification of many serotonin receptor types has stimulated the search for the role of serotonin in the pathogenesis of anxiety disorders. Different types of acute stress result in increased 5-

hydroxytryptamine (5-HT) turnover in the prefrontal cortex, nucleus accumbens, amygdala, and lateral hypothalamus. The interest in this relation was initially motivated by the observation that serotonergic antidepressants have therapeutic effects in some anxiety disorders—for example, clomipramine (Anafranil) in obsessive-compulsive disorder (OCD). The effectiveness of buspirone (BuSpar), a serotonin 5-HT1A receptor agonist, in the treatment of anxiety disorders also suggests the possibility of an association between serotonin and anxiety. The cell bodies of most serotonergic neurons are located in the raphe nuclei in the rostral brainstem and project to the cerebral cortex, the limbic system (especially, the amygdala and the hippocampus), and the hypothalamus. Several reports indicate that metachlorophenylpiperazine (mCPP), a drug with multiple serotonergic and nonserotonergic effects, and fenfluramine (Pondimin), which causes the release of serotonin, do cause increased anxiety in patients with anxiety disorders; and many anecdotal reports indicate that serotonergic hallucinogens and stimulants—for example, lysergic acid diethylamide (LSD) and 3,4-methylenedioxymethamphetamine (MDMA)—are associated with the development of both acute and chronic anxiety disorders in persons who use these drugs. Clinical studies of 5-HT function in anxiety disorders have had mixed results. One study found that patients with panic disorder had lower levels of circulating 5-HT compared with control participants. Thus, no clear pattern of abnormality in 5-HT function in panic disorder has emerged from analysis of peripheral blood elements. GABA. A role of GABA in anxiety disorders is most strongly supported by the undisputed efficacy of benzodiazepines, which enhance the activity of GABA at the GABA type A (GABAA) receptor, in the treatment of some types of anxiety disorders. Although lowpotency benzodiazepines are most effective for the symptoms of generalized anxiety disorder, high-potency benzodiazepines, such as alprazolam (Xanax), and clonazepam are effective in the treatment of panic disorder. Studies in primates have found that autonomic nervous system symptoms of anxiety disorders are induced when a

benzodiazepine inverse agonist, β-carboline-3-carboxylic acid (BCCE), is administered. BCCE also causes anxiety in normal control volunteers. A benzodiazepine antagonist, flumazenil (Romazicon), causes frequent severe panic attacks in patients with panic disorder. These data have led researchers to hypothesize that some patients with anxiety disorders have abnormal functioning of their GABAA receptors, although this connection has not been shown directly. APLYSIA. A neurotransmitter model for anxiety disorders is based on the study of Aplysia californica by Nobel Prize winner Eric Kandel, M.D. Aplysia is a sea snail that reacts to danger by moving away, withdrawing into its shell, and decreasing its feeding behavior. These behaviors can be classically conditioned, so that the snail responds to a neutral stimulus as if it were a dangerous stimulus. The snail can also be sensitized by random shocks, so that it exhibits a flight response in the absence of real danger. Parallels have previously been drawn between classic conditioning and human phobic anxiety. The classically conditioned Aplysia shows measurable changes in presynaptic facilitation, resulting in the release of increased amounts of neurotransmitter. Although the sea snail is a simple animal, this work shows an experimental approach to complex neurochemical processes potentially involved in anxiety disorders in humans. NEUROPEPTIDE Y. Neuropeptide Y (NPY) is a highly conserved 36–amino acid peptide, which is among the most abundant peptides found in mammalian brain. Evidence suggesting the involvement of the amygdala in the anxiolytic effects of NPY is robust, and it probably occurs via the NPY-Y1 receptor. NPY has counterregulatory effects on corticotropin-releasing hormone (CRH) and LC-NE systems at brain sites that are important in the expression of anxiety, fear, and depression. Preliminary studies in special operations soldiers under extreme training stress indicate that high NPY levels are associated with better performance.

GALANIN. Galanin is a peptide that, in humans, contains 30 amino acids. It has been demonstrated to be involved in a number of physiological and behavioral functions, including learning and memory, pain control, food intake, neuroendocrine control, cardiovascular regulation, and, most recently, anxiety. A dense galanin immunoreactive fiber system originating in the LC innervates forebrain and midbrain structures, including the hippocampus, hypothalamus, amygdala, and prefrontal cortex. Studies in rats have shown that galanin administered centrally modulates anxiety-related behaviors. Galanin and NPY receptor agonists may be novel targets for antianxiety drug development. Brain Imaging Studies. A range of brain imaging studies, almost always conducted with a specific anxiety disorder, has produced several possible leads in the understanding of anxiety disorders. Structural studies—for example, computed tomography (CT) and magnetic resonance imaging (MRI)—occasionally show some increase in the size of cerebral ventricles. In one study, the increase was correlated with the length of time patients had been taking benzodiazepines. In one MRI study, a

specific defect in the right temporal lobe was noted in patients with panic disorder. Several other brain imaging studies have reported abnormal findings in the right hemisphere but not the left hemisphere; this finding suggests that some types of cerebral asymmetries may be important in the development of anxiety disorder symptoms in specific patients. Functional brain imaging (fMRI) studies—for example, positron emission tomography (PET), single-photon emission computed tomography (SPECT), and electroencephalography (EEG)—of patients with anxiety disorder have variously reported abnormalities in the frontal cortex; the occipital and temporal areas; and, in a study of panic disorder, the parahippocampal gyrus. Several functional neuroimaging studies have implicated the caudate nucleus in the pathophysiology of OCD. In posttraumatic stress disorder, fMRI studies have found increased activity in the amygdala, a brain region associated with fear (see Color Plate 9.1-1). A conservative interpretation of these data is that some patients with anxiety disorders have a demonstrable functional cerebral pathological condition and that the condition may be causally relevant to their anxiety disorder symptoms. Genetic Studies. Genetic studies have produced solid evidence that at least some genetic component contributes to the development of anxiety disorders. Heredity has been recognized as a predisposing factor in the development of anxiety disorders. Almost half of all patients with panic disorder have at least one affected relative. The figures for other anxiety disorders, although not as high, also indicate a higher frequency of the illness in first-degree relatives of affected patients than in the relatives of nonaffected persons. Although adoption studies with anxiety disorders have not been reported, data from twin registries also support the hypothesis that anxiety disorders are at least partially genetically determined. Clearly, a linkage exists between genetics and anxiety disorders, but no anxiety disorder is likely to result from a simple mendelian abnormality. One report has attributed about 4 percent of the intrinsic variability of anxiety within the general population to a polymorphic variant of the gene for the serotonin transporter, which is the site of action of many serotonergic drugs. Persons with the variant produce less transporter and have higher levels of anxiety. In 2005, a scientific team, led by National Institute of Mental Health grantee and Noble Laureate Dr. Eric Kandel demonstrated that knocking out a gene in the brain’s fear hub creates mice unperturbed by situations that would normally trigger instinctive or learned fear responses. The gene codes for stathmin, a protein that is critical for the amygdala to form fear memories. Stathmin knockout mice showed less anxiety when they heard a tone that had previously been associated with a shock, indicating less learned fear. The knockout mice also were more susceptible to explore novel open space and maze environments, a reflection of less innate fear. Kandel suggests that stathmin

knockout mice can be used as a model of anxiety states of mental disorders with innate and learned fear components: these animals could be used to develop new antianxiety agents. Whether stathmin is similarly expressed and pivotal for anxiety in the human amygdala remains to be confirmed. Neuroanatomical Considerations. The locus ceruleus and the raphe nuclei project primarily to the limbic system and the cerebral cortex. In combination with the

data from brain imaging studies, these areas have become the focus of much hypothesisforming about the neuroanatomical substrates of anxiety disorders. LIMBIC SYSTEM. In addition to receiving noradrenergic and serotonergic innervation, the limbic system also contains a high concentration of GABAA receptors. Ablation and stimulation studies in nonhuman primates have also implicated the limbic system in the generation of anxiety and fear responses. Two areas of the limbic system have received special attention in the literature: increased activity in the septohippocampal pathway, which may lead to anxiety; and the cingulate gyrus, which has been implicated particularly in the pathophysiology of OCD. CEREBRAL CORTEX. The frontal cerebral cortex is connected with the parahippocampal region, the cingulate gyrus, and the hypothalamus and thus may be involved in the production of anxiety disorders. The temporal cortex has also been implicated as a pathophysiological site in anxiety disorders. This association is based in part on the similarity in clinical presentation and electrophysiology between some patients with temporal lobe epilepsy and patients with OCD. REFERENCES Bulbena A, Gago J, Pailhez G, Sperry L, Fullana MA, Vilarroya O. Joint hypermobility syndrome is a risk factor trait for anxiety disorders: A 15-year follow-up cohort study. Gen Hosp Psychiatry. 2011;33:363. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? Depress Anxiety. 2009;26:1066. Fergus TA, Valentiner DP, McGrath PB, Jencius S. Shame- and guilt-proneness: Relationships with anxiety disorder symptoms in a clinical sample. J Anxiety Disord. 2010;24:811. Goodwin RD, Stein DJ. Anxiety disorders and drug dependence: Evidence on sequence and specificity among adults. Psych Clin Neurosci. 2013;67:167. Kravitz HM, Schott LL, Joffe H, Cyranowski JM, Bromberger JT. Do anxiety symptoms predict major depressive disorder in midlife women? The Study of Women's Health Across the Nation (SWAN) Mental Health Study (MHS). Psychol Med. 2014:1–10. McKay D, Storch EA, eds. Handbook of Treating Variants and Complications in Anxiety Disorders. New York: Springer Science+Business Media; 2013. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res. 2011;45:1027. Naragon-Gainey K, Gallagher MW, Brown TA. A longitudinal examination of psychosocial impairment across the anxiety disorders. Psycholog Med. 2013;43:1475. Nebel-Schwalm MS, Davis III TE. Nature and etiological models of anxiety disorders. In: McKay D, Storch EA, eds. Handbook of Treating Variants and Complications in Anxiety Disorders. New York: Springer Science+Business Media; 2013:3. Pacheco-Unguetti AP, Acosta A, Marqués E, Lupiáñez J. Alterations of the attentional networks in patients with anxiety disorders. J Anxiety Disord. 2011;25:888. Pine DS. Anxiety disorders: Introduction and overview. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1839.

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Schanche E. The transdiagnostic phenomenon of self-criticism. Psychotherapy. 2013;50:316. Shin LM, Davis FC, Van Elzakker MB, Dahlgren MK, Dubois SJ. Neuroimaging predictors of treatment response in anxiety disorders. Bio Mood Anxiety Dis. 2013;3:15. Stein DJ, Hollander E, Rothbaum BO, eds. Textbook of Anxiety Disorders. 2nd edition. Arlington, VA: American Psychiatric Publishing; 2009. Stein DJ, Nesse RM. Threat detection, precautionary responses, and anxiety disorders. Neurosci Biobehav Rev. 2011;35:1075. Taylor S, Abramowitz JS, McKay D. Non-adherence and non-response in the treatment of anxiety disorders. J Anxiety Disord. 2012;26:583. Uebelacker L, Weisberg R, Millman M, Yen S, Keller M. Prospective study of risk factors for suicidal behavior in individuals with anxiety disorders. Psychological Med. 2013;43:1465. 9.2 Panic Disorder An acute intense attack of anxiety accompanied by feelings of impending doom is known as panic disorder. The anxiety is characterized by discrete periods of intense fear that can vary from several attacks during one day to only a few attacks during a year. Patients with panic disorder present with a number of comorbid conditions, most commonly agoraphobia, which refers to a fear of or anxiety regarding places from which escape might be difficult. HISTORY The idea of panic disorder may have its roots in the concept of irritable heart syndrome, which the physician Jacob Mendes DaCosta (1833–1900) noted in soldiers in the American Civil War. DaCosta’s syndrome included many psychological and somatic symptoms that have since been included among the diagnostic criteria for panic disorder. In 1895, Sigmund Freud introduced the concept of anxiety neurosis, consisting of acute and chronic psychological and somatic symptoms. EPIDEMIOLOGY The lifetime prevalence of panic disorder is in the 1 to 4 percent range, with 6-month prevalence approximately 0.5 to 1.0 percent and 3 to 5.6 percent for panic attacks. Women are two to three times more likely to be affected than men, although underdiagnosis of panic disorder in men may contribute to the skewed distribution. The differences among Hispanics, whites, and blacks are few. The only social factor identified as contributing to the development of panic disorder is a recent history of divorce or separation. Panic disorder most commonly develops in young adulthood—the mean age of presentation is about 25 years—but both panic disorder and agoraphobia can develop at any age. Panic disorder has been reported in children and adolescents, and it is probably underdiagnosed in these age groups.

COMORBIDITY Of patients with panic disorder, 91 percent have at least one other psychiatric disorder. About one-third of persons with panic disorders have major depressive disorder before onset; about two-thirds first experience panic disorder during or after the onset of major depression. Other disorders also commonly occur in persons with panic disorder. Of persons with panic disorder, 15 to 30 percent also have social anxiety disorder or social phobia, 2 to 20 percent have specific phobia, 15 to 30 percent have generalized anxiety disorder, 2 to 10 percent have PTSD, and up to 30 percent have OCD. Other common comorbid conditions are hypochondriasis or

illness anxiety disorder, personality disorders, and substance-related disorders. ETIOLOGY Biological Factors Research on the biological basis of panic disorder has produced a range of findings; one interpretation is that the symptoms of panic disorder are related to a range of biological abnormalities in brain structure and function. Most work has used biological stimulants to induce panic attacks in patients with panic disorder. Considerable evidence indicates that abnormal regulation of brain noradrenergic systems is also involved in the pathophysiology of panic disorder. These and other studies have produced hypotheses implicating both peripheral and central nervous system (CNS) dysregulation in the pathophysiology of panic disorder. The autonomic nervous systems of some patients with panic disorder have been reported to exhibit increased sympathetic tone, to adapt slowly to repeated stimuli, and to respond excessively to moderate stimuli. Studies of the neuroendocrine status of these patients have shown several abnormalities, although the studies have been inconsistent in their findings. The major neurotransmitter systems that have been implicated are those for norepinephrine, serotonin, and GABA. Serotonergic dysfunction is quite evident in panic disorder, and various studies with mixed serotonin agonist–antagonist drugs have demonstrated increased rates of anxiety. Such responses may be caused by postsynaptic serotonin hypersensitivity in panic disorder. Preclinical evidence suggests that attenuation of local inhibitory GABAergic transmission in the basolateral amygdala, midbrain, and hypothalamus can elicit anxiety-like physiological responses. The biological data have led to a focus on the brainstem (particularly the noradrenergic neurons of the locus ceruleus and the serotonergic neurons of the median raphe nucleus), the limbic system (possibly responsible for the generation of anticipatory anxiety), and the prefrontal cortex (possibly responsible for the generation of phobic avoidance). Among the various neurotransmitters involved, the noradrenergic system has also attracted much attention, with the presynaptic α2-adrenergic receptors, particularly, playing a significant role. Patients with panic disorder are sensitive to the

anxiogenic effects of yohimbine in addition to having exaggerated MHPG, cortisol, and cardiovascular responses. They have been identified by pharmacological challenges with the α2-receptor agonist clonidine (Catapres) and the α2-receptor antagonist yohimbine (Yocon), which stimulates firing of the locus ceruleus and elicits high rates of panic-like activity in those with panic disorder. Panic-Inducing Substances. Panic-inducing substances (sometimes called panicogens) induce panic attacks in most patients with panic disorder and in a much smaller proportion of persons without panic disorder or a history of panic attacks. Socalled respiratory panic-inducing substances cause respiratory stimulation and a shift in the acid–base balance. These substances include carbon dioxide (5 to 35 percent mixtures), sodium lactate, and bicarbonate. Neurochemical panic-inducing substances that act through specific neurotransmitter systems include yohimbine, an α2-adrenergic receptor antagonist; mCPP, an agent with multiple serotonergic effects; m-Caroline drugs; GABAB receptor inverse agonists; flumazenil (Romazicon), a GABAB receptor antagonist; cholecystokinin; and caffeine. Isoproterenol (Isuprel) is also a panicinducing substance, although its mechanism of action in inducing panic attacks is poorly understood. The respiratory panic-inducing substances may act initially at the peripheral cardiovascular baroreceptors and relay their signal by vagal afferents to the nucleus tractus solitarii and then on to the nucleus paragigantocellularis of the medulla. The hyperventilation in patients with panic disorder may be caused by a hypersensitive suffocation alarm system whereby increasing $PCO_2$ and brain lactate concentrations prematurely activate a physiological asphyxia monitor. The neurochemical panicinducing substances are presumed to primarily affect the noradrenergic, serotonergic, and GABA receptors of the CNS directly. Brain Imaging. Structural brain imaging studies, for example,

MRI, in patients with panic disorder have implicated pathological involvement in the temporal lobes, particularly the hippocampus and the amygdala. One MRI study reported abnormalities, especially cortical atrophy, in the right temporal lobe of these patients. Functional brain imaging studies, for example, positron emission tomography (PET), have implicated dysregulation of cerebral blood flow (smaller increase or an actual decrease in cerebral blood flow). Specifically, anxiety disorders and panic attacks are associated with cerebral vasoconstriction, which may result in CNS symptoms, such as dizziness, and in peripheral nervous system symptoms that may be induced by hyperventilation and hypocapnia. Most functional brain imaging studies have used a specific panic-inducing substance (e.g., lactate, caffeine, or yohimbine) in combination with PET or SPECT to assess the effects of the panic-inducing substance and the induced panic attack on cerebral blood flow. Mitral Valve Prolapse. Although great interest was formerly expressed in an association between mitral valve prolapse and panic disorder, research has almost

completely erased any clinical significance or relevance to the association. Mitral valve prolapse is a heterogeneous syndrome consisting of the prolapse of one of the mitral valve leaflets, resulting in a midsystolic click on cardiac auscultation. Studies have found that the prevalence of panic disorder in patients with mitral valve prolapse is the same as the prevalence of panic disorder in patients without mitral valve prolapse. Genetic Factors Various studies have found that the first-degree relatives of patients with panic disorder have a four- to eightfold higher risk for panic disorder than first-degree relatives of other psychiatric patients. The twin studies conducted to date have generally reported that monozygotic twins are more likely to be concordant for panic disorder than are dizygotic twins. At this point, no data exist indicating an association between a specific chromosomal location or mode of transmission and this disorder. Psychosocial Factors Psychoanalytic theories have been developed to explain the pathogenesis of panic disorder. Psychoanalytic theories conceptualize panic attacks as arising from an unsuccessful defense against anxiety-provoking impulses. What was previously a mild signal anxiety becomes an overwhelming feeling of apprehension, complete with somatic symptoms. Many patients describe panic attacks as coming out of the blue, as though no psychological factors were involved, but psychodynamic exploration frequently reveals a clear psychological trigger for the panic attack. Although panic attacks are correlated neurophysiologically with the locus ceruleus, the onset of panic is generally related to environmental or psychological factors. Patients with panic disorder have a higher incidence of stressful life events (particularly loss) than control subjects in the months before the onset of panic disorder. Moreover, the patients typically experience greater distress about life events than control subjects do. The hypothesis that stressful psychological events produce neurophysiological changes in panic disorder is supported by a study of female twins. Separation from the mother early in life was clearly more likely to result in panic disorder than was paternal separation in the cohort of 1,018 pairs of female twins. Another etiological factor in adult female patients appears to be childhood physical and sexual abuse. Approximately 60 percent of women with panic disorder have a history of childhood sexual abuse compared with 31 percent of women with other anxiety disorders. Further support for psychological mechanisms in panic disorder can be inferred from a study of panic disorder in which patients received successful treatment with cognitive therapy. Before the therapy, the patients responded to panic attack induction with lactate. After successful cognitive therapy, lactate infusion no longer produced a panic attack. The research indicates that the cause of panic attacks is likely to involve the unconscious meaning of stressful events and that the pathogenesis of the panic attacks may be related to neurophysiological factors triggered by the psychological reactions.

Psychodynamic clinicians should always thoroughly investigate possible triggers whenever assessing a patient with panic disorder. The psychodynamics of panic disorder are summarized in Table 9.2-1. Table 9.2-1 Psychodynamic Themes in Panic Disorder DIAGNOSIS Panic Attacks A panic attack is a sudden period of intense fear or apprehension that may last from minutes to hours. Panic attacks can occur in mental disorders other than panic disorder, particularly in specific phobia, social phobia, and PTSD. Unexpected panic attacks occur at any time and are not associated with any identifiable situational stimulus, but panic attacks need not be unexpected. Attacks in patients with social and specific phobias are usually expected or cued to a recognized or specific stimulus. Some panic attacks do not fit easily into the distinction between unexpected and expected, and these attacks are referred to as situationally predisposed panic attacks. They may or may not occur when a patient is exposed to a specific trigger, or they may occur either immediately after exposure or after a considerable delay. Panic Disorder The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for panic disorder are listed in Table 9.2-2. Some community surveys have indicated that panic attacks are common, and a major issue in developing diagnostic criteria for panic disorder was determining a threshold number or frequency of panic attacks required to meet the diagnosis. Setting the threshold too low results in the diagnosis of panic disorder in patients who do not have an impairment from an

occasional panic attack; setting the threshold too high results in a situation in which patients who are impaired by their panic attacks do not meet the diagnostic criteria. Table 9.2-2 DSM-5 Diagnostic Criteria for Panic Disorder

CLINICAL FEATURES The first panic attack is often completely spontaneous, although panic attacks occasionally follow excitement, physical exertion, sexual activity, or moderate

emotional trauma. Clinicians should attempt to ascertain any habit or situation that commonly precedes a patient’s panic attacks. Such activities may include the use of caffeine, alcohol, nicotine, or other substances; unusual patterns of sleeping or eating; and specific environmental settings, such as harsh lighting at work. The attack often begins with a 10-minute period of rapidly increasing symptoms. The major mental symptoms are extreme fear and a sense of impending death and doom. Patients usually cannot name the source of their fear; they may feel confused and have trouble concentrating. The physical signs often include tachycardia, palpitations, dyspnea, and sweating. Patients often try to leave whatever situation they are in to seek help. The attack generally lasts 20 to 30 minutes and rarely more than an hour. A formal mental status examination during a panic attack may reveal rumination, difficulty speaking (e.g., stammering), and impaired memory. Patients may experience depression or depersonalization during an attack. The symptoms can disappear quickly or gradually. Between attacks, patients may have anticipatory anxiety about having another attack. The differentiation between anticipatory anxiety and generalized anxiety disorder can be difficult, although patients with pain disorder with anticipatory anxiety can name the focus of their anxiety. Somatic concerns of death from a cardiac or respiratory problem may be the major focus of patients’ attention during panic attacks. Patients may believe that the palpitations and chest pain indicate that they are about to die. As many as 20 percent of such patients actually have syncopal episodes during a panic attack. The patients may be seen in emergency departments as young (20s), physically healthy persons who nevertheless insist that they are about to die from a heart attack. Rather than immediately diagnosing hypochondriasis, the emergency department physician should consider a diagnosis of panic disorder.

Hyperventilation can produce respiratory alkalosis and other symptoms. The age-old treatment of breathing into a paper bag sometimes helps because it decreases alkalosis. Mrs. K was a 35-year-old woman who initially presented for treatment at the medical emergency department at a large university-based medical center. She reported that while sitting at her desk at her job, she had suddenly experienced difficulty breathing, dizziness, tachycardia, shakiness, and a feeling of terror that she was going to die of a heart attack. A colleague drove her to the emergency department, where she received a full medical evaluation, including electrocardiography and routine blood work, which revealed no sign of cardiovascular, pulmonary, or other illness. She was subsequently referred for psychiatric evaluation, where she revealed that she had experienced two additional episodes over the past month, once when driving home from work and once when eating breakfast. However, she had not presented for medical treatment because the symptoms had resolved relatively quickly each time, and she worried that if she went to the hospital without ongoing symptoms, “people would think I’m crazy.” Mrs. K reluctantly took the phone number of a local psychiatrist but did not call until she

experienced a fourth episode of a similar nature. (Courtesy of Erin B. McClure-Tone, Ph.D., and Daniel S. Pine, M.D.) Associated Symptoms Depressive symptoms are often present in panic disorder, and in some patients, a depressive disorder coexists with the panic disorder. Some studies have found that the lifetime risk of suicide in persons with panic disorder is higher than it is in persons with no mental disorder. Clinicians should be alert to the risk of suicide. In addition to agoraphobia, other phobias and OCD can coexist with panic disorder. The psychosocial consequences of panic disorder, in addition to marital discord, can include time lost from work, financial difficulties related to the loss of work, and alcohol and other substance abuse. DIFFERENTIAL DIAGNOSIS Panic Disorder The differential diagnosis for a patient with panic disorder includes many medical disorders (Table 9.2-3), as well as many mental disorders. Table 9.2-3 Organic Differential Diagnosis for Panic Disorder

Medical Disorders Panic disorder must be differentiated from a number of medical conditions that produce similar symptomatology. Panic attacks are associated with a variety of endocrinological disorders, including both hypo- and hyperthyroid states, hyperparathyroidism, and pheochromocytomas. Episodic hypoglycemia associated with insulinomas can also produce panic-like states, as can primary neuropathological processes. These include seizure disorders, vestibular dysfunction, neoplasms, or the effects of both prescribed and illicit substances on the CNS. Finally, disorders of the cardiac and pulmonary systems, including arrhythmias, chronic obstructive pulmonary disease, and asthma, can produce autonomic symptoms and accompanying crescendo anxiety that can be difficult

to distinguish from panic disorder. Clues of an underlying medical etiology to panic-like symptoms include the presence of atypical features during panic attacks, such as ataxia, alterations in consciousness, or bladder dyscontrol; onset of panic disorder relatively late in life; and physical signs or symptoms indicative of a medical disorder. Mental Disorders Panic disorder also must be differentiated from a number of psychiatric disorders, particularly other anxiety disorders. Panic attacks occur in many anxiety disorders, including social and specific phobia, Panic may also occur in PTSD and OCD. The key to correctly diagnosing panic disorder and differentiating the condition from other anxiety disorders involves the documentation of recurrent spontaneous panic attacks at some point in the illness. Differentiation from generalized anxiety disorder can also be difficult.

Classically, panic attacks are characterized by their rapid onset (within minutes) and short duration (usually less than 10 to 15 minutes), in contrast to the anxiety associated with generalized anxiety disorder, which emerges and dissipates more slowly. Making this distinction can be difficult, however, because the anxiety surrounding panic attacks can be more diffuse and slower to dissipate than is typical. Because anxiety is a frequent concomitant of many other psychiatric disorders, including the psychoses and affective disorders, discrimination between panic disorder and a multitude of disorders can also be difficult. Specific and Social Phobias Sometimes it is difficult to distinguish between panic disorder, on the one hand, and specific and social phobias, on the other hand. Some patients who experience a single panic attack in a specific setting (e.g., an elevator) may go on to have long-lasting avoidance of the specific setting, regardless of whether they ever have another panic attack. These patients meet the diagnostic criteria for a specific phobia, and clinicians must use their judgment about what is the most appropriate diagnosis. In another example, a person who experiences one or more panic attacks may then fear speaking in public. Although the clinical picture is almost identical to the clinical picture in social phobia, a diagnosis of social phobia is excluded because the avoidance of the public situation is based on fear of having a panic attack rather than on fear of the public speaking itself. COURSE AND PROGNOSIS Panic disorder usually has its onset in late adolescence or early adulthood, although onset during childhood, early adolescence, and midlife does occur. Some data implicate increased psychosocial stressors with the onset of panic disorder, although no psychosocial stressor can be definitely identified in most cases. Panic disorder, in general, is a chronic disorder, although its course is variable, both among patients and within a single patient. The available long-term follow-up studies of

panic disorder are difficult to interpret because they have not controlled for the effects of treatment. Nevertheless, about 30 to 40 percent of patients seem to be symptom free at long-term follow-up, about 50 percent have symptoms that are sufficiently mild not to affect their lives significantly, and about 10 to 20 percent continue to have significant symptoms. After the first one or two panic attacks, patients may be relatively unconcerned about their condition; with repeated attacks, however, the symptoms may become a major concern. Patients may attempt to keep the panic attacks secret and thereby cause their families and friends concern about unexplained changes in behavior. The frequency and severity of the attacks can fluctuate. Panic attacks can occur several times in a day or less than once a month. Excessive intake of caffeine or nicotine can exacerbate the symptoms. Depression can complicate the symptom picture in anywhere from 40 to 80 percent of all patients, as estimated by various studies. Although the patients do not tend to talk about suicidal ideation, they are at increased risk for committing suicide. Alcohol and other substance dependence occurs in about 20 to 40 percent of all patients, and OCD may also develop. Family interactions and performance in school and at work commonly suffer. Patients with good premorbid functioning and symptoms of brief duration tend to have good prognoses. TREATMENT With treatment, most patients exhibit dramatic improvement in the symptoms of panic disorder and agoraphobia. The two most effective treatments are pharmacotherapy and cognitive-behavioral therapy. Family and group therapy may help affected patients and their families adjust to the patient’s disorder and to the psychosocial difficulties that the disorder may have precipitated. Pharmacotherapy Overview. Alprazolam (Xanax) and paroxetine (Paxil) are the two drugs approved by the US Food and Drug Administration (FDA) for the treatment of panic disorder. In general, experience is showing superiority of the selective serotonin reuptake inhibitors (SSRIs) and clomipramine (Anafranil) over the benzodiazepines, monoamine oxidase inhibitors (MAOIs),

and tricyclic and tetracyclic drugs in terms of effectiveness and tolerance of adverse effects. Some reports have suggested a role for venlafaxine (Effexor), and buspirone (BuSpar) has been suggested as an additive medication in some cases. Venlafaxine is approved by the FDA for treatment of generalized anxiety disorder and may be useful in panic disorder combined with depression. β-adrenergic receptor antagonists have not been found to be particularly useful for panic disorder. A conservative approach is to begin treatment with paroxetine, sertraline (Zoloft), citalopram (Celexa), or fluvoxamine (Luvox) in isolated panic disorder. If rapid control of severe symptoms is desired, a brief course of alprazolam should be initiated

concurrently with the SSRI followed by slowly tapering use of the benzodiazepine. In long-term use, fluoxetine (Prozac) is an effective drug for panic with comorbid depression, although its initial activating properties may mimic panic symptoms for the first several weeks, and it may be poorly tolerated on this basis. Clonazepam (Klonopin) can be prescribed for patients who anticipate a situation in which panic may occur (0.5 to 1 mg as required). Common dosages for antipanic drugs are listed in Table 9.2-4. Table 9.2-4 Recommended Dosages for Antipanic Drugs (Daily Unless Indicated Otherwise)

Selective Serotonin Reuptake Inhibitors. All SSRIs are effective for panic disorder. Paroxetine and paroxetine CR have sedative effects and tend to calm patients immediately, which leads to greater compliance and less discontinuation, but this must be weighed against its weight gain potential. Citalopram, escitalopram (Lexapro), fluvoxamine, and sertraline are the next best tolerated. Anecdotal reports suggest that patients with panic disorder are particularly sensitive to the activating effects of SSRIs, particularly fluoxetine, so they should be given initially at small dosages and titrated up slowly. At therapeutic dosages—for example, 20 mg a day of paroxetine—some patients may experience increased sedation. One approach for patients with panic disorder is to give 5 or 10 mg a day of paroxetine or 12.5 to 25 mg of paroxetine CR for 1 to 2 weeks and then increase the dosage by 10 mg of paroxetine or 12.5 mg of paroxetine CR a day every 1 to 2 weeks to a maximum of 60 mg of paroxetine or 62.5 mg of paroxetine CR. If sedation becomes intolerable, then taper the paroxetine dosage down to 10 mg a day of paroxetine or 12.5 mg of paroxetine CR and switch to fluoxetine at 10 mg a day and titrate upward slowly. Other strategies can be used based on the experience of the clinician. Benzodiazepines. Benzodiazepines have the most rapid onset of action against panic, often within the first week, and they can be used for long periods without the development of tolerance to the antipanic effects. Alprazolam has been the most widely used benzodiazepine for panic disorder, but controlled studies have demonstrated equal efficacy for lorazepam (Ativan), and case reports have also indicated that clonazepam may be effective. Some patients use benzodiazepines as needed when faced with a phobic stimulus. Benzodiazepines can reasonably be used as the first agent for treatment of panic disorder while a serotonergic drug is being slowly titrated to a therapeutic dose. After 4 to 12 weeks, benzodiazepine use can be slowly tapered (over 4 to 10 weeks) while the serotonergic drug is continued. The major reservation among clinicians regarding the use of benzodiazepines for panic disorder is the potential for dependence, cognitive impairment, and abuse, especially after long-term use. Patients should be instructed not to drive, abstain from alcohol or other CNS depressant medications, and avoid operating dangerous equipment while taking benzodiazepines. Whereas benzodiazepines elicit a sense of well-being, discontinuation of benzodiazepines produces a well-documented and unpleasant withdrawal syndrome. Anecdotal reports and small case series have indicated that addiction to alprazolam is one of the most difficult to overcome, and it may require a

comprehensive program of detoxification. Benzodiazepine dosage should be tapered slowly, and all anticipated withdrawal effects should be thoroughly explained to the patient. Tricyclic and Tetracyclic Drugs. At the present time, SSRIs are considered the first-line agents for the treatment of panic disorder. Data, however, show that among tricyclic drugs, clomipramine and imipramine (Tofranil) are the most effective in the treatment of panic disorder. Clinical experience indicates that the dosages must be titrated slowly upward to avoid overstimulation and that the full clinical benefit

requires full dosages and may not be achieved for 8 to 12 weeks. Some data support the efficacy of desipramine (Norpramin), and less evidence suggests a role for maprotiline (Ludiomil), trazodone (Desyrel), nortriptyline (Pamelor), amitriptyline (Elavil), and doxepin (Adapin). Tricyclic drugs are less widely used than SSRIs because the tricyclic drugs generally have more severe adverse effects at the higher dosages required for effective treatment of panic disorder. Monoamine Oxidase Inhibitors. The most robust data support the effectiveness of phenelzine (Nardil), and some data also support the use of tranylcypromine (Parnate). MAOIs appear less likely to cause overstimulation than either SSRIs or tricyclic drugs, but they may require full dosages for at least 8 to 12 weeks to be effective. The need for dietary restrictions has limited the use of MAOIs, particularly since the appearance of the SSRIs. Treatment Nonresponse. If patients fail to respond to one class of drugs, another should be tried. Recent data support the effectiveness of venlafaxine. The combination of an SSRI or a tricyclic drug and a benzodiazepine or of an SSRI and lithium or a tricyclic drug can be tried. Case reports have suggested the effectiveness of carbamazepine (Tegretol), valproate (Depakene), and calcium channel inhibitors. Buspirone may have a role in the augmentation of other medications but has little effectiveness by itself. Clinicians should reassess the patient, particularly to establish the presence of comorbid conditions such as depression, alcohol use, or other substance use. Duration of Pharmacotherapy. When it becomes effective, pharmacological treatment should generally continue for 8 to 12 months. Data indicate that panic disorder is a chronic, perhaps lifelong, condition that recurs when treatment is discontinued. Studies have reported that 30 to 90 percent of patients with panic disorder who have had successful treatment have a relapse when their medication is discontinued. Patients may be likely to relapse if they have been given benzodiazepines and the benzodiazepine therapy is terminated in a way that causes withdrawal symptoms. Cognitive and Behavior Therapies Cognitive and behavior therapies are effective treatments for panic disorder. Various reports have concluded that cognitive and behavior therapies are superior to pharmacotherapy alone; other reports have concluded the opposite. Several studies and reports have found that the combination of cognitive or behavior therapy with pharmacotherapy is more effective than either approach alone. Several studies that included long-term follow-up of patients who received cognitive or behavior therapy indicate that the therapies are effective in producing long-lasting remission of symptoms.

Cognitive Therapy. The two major foci of cognitive therapy for panic disorder are instruction about a patient’s false beliefs and information about panic attacks. The instruction about false beliefs centers on the patient’s tendency to misinterpret mild bodily sensations as indicating impending panic attacks, doom, or death. The information about panic attacks includes explanations that when panic attacks occur, they are time limited and not life threatening. REFERENCES Cougle JR, Feldner MT, Keough ME, Hawkins KA, Fitch KE. Comorbid panic attacks among individuals with posttraumatic stress disorder: Associations with traumatic event exposure history, symptoms, and impairment. J Anxiety Disord. 2010;24:183. Fentz HN, Hoffart A, Jensen MB, Arendt M, O’Toole MS,

Rosenberg NK, Hougaard E. Mechanisms of change in cognitive behaviour therapy for panic disorder: the role of panic self-efficacy and catastrophic misinterpretations. Behav Res Ther. 2013;51:579–587. Funayama T, Furukawa TA, Nakano Y, Noda Y, Ogawa S, Watanabe N, Chen J, Noguchi Y. In-situation safety behaviors among patients with panic disorder: descriptive and correlational study. Psych Clin Neurosci. 2013;67:332–339. Hodges LM, Fyer AJ, Weissman MM, Logue MW, Haghighi F, Evgrafov O, Rotondo A, Knowles JA, Hamilton SP. Evidence for Linkage and Association of GABRB3 and GABRA5 to Panic Disorder. Neuropsychopharmacology. 2014. McClure-Tone EB, Pine DS. Clinical features of the anxiety disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1844. McTeague LM, Lang PJ, Laplante MC, Bradley MM. Aversive imagery in panic disorder: Agoraphobia severity, comorbidity, and defensive physiology. Biol Psychiatry. 2011;70:415. Nardi AE, Valença AM, Freire RC, Amrein R, Sardinha A, Levitan MN, Nascimento I, de-Melo-Neto VL, King AL, de O. e Silva AC, Veras AB, Dias GP, Soares-Filho GL, da Costa RT, Mezzasalma MA, de Carvalho MR, de Cerqueira AC, Hallak JE, Crippa JA, Versiani M. Randomized, open naturalistic, acute treatment of panic disorder with clonazepam or paroxetine. J Clin Psychopharmacol. 2011;31:259. Noel JM, Curtis JL. The pharmacological management of stress reactions. In: Everly GS Jr, Lating JM. A Clinical Guide to the Treatment of the Human Stress Response. New York: Springer Science+Business Media; 2013:317. Onur E, Alkın T, Sheridan MJ, Wise TN. Alexithymia and emotional intelligence in patients with panic disorder, generalized anxiety disorder and major depressive disorder. Psych Quart. 2013;84:303. Otto MW, Tolin DF, Simon NM, Pearlson GD, Basden S, Meunier SA, Hofmann SG, Eisenmenger K, Krystal JH, Pollack MH. Efficacy of D-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. Biol Psychiatry. 2010;67:365. Pilecki B, Arentoft A, McKay D. An evidence-based causal model of panic disorder. J Anxiety Disord. 2011;25:381. Spatola CAM, Scaini S, Pesenti-Gritti P, Medland SE, Moruzzi S, Ogliari A, Tambs K, Battaglia M. Gene–environment interactions in panic disorder and CO2 sensitivity: Effects of events occurring early in life. Am J Med Gen. 2011;156:79. Thorpe GL, Sigmon ST, Yoon KL. Agoraphobia and panic disorder. In: Ramachandran VS, ed. Encyclopedia of Human Behavior. 2nd edition. Burlington, MA: Academic Press; 2012:68. Wuyek LA, Antony MM, McCabe RE. Psychometric properties of the panic disorder severity scale: Clinician-administered and self-report versions. Clin Psychol Psychother. 2011;18:234.

# 03 - 9.3 Agoraphobia

# 9.3 Agoraphobia

9.3 Agoraphobia Agoraphobia refers to a fear of or anxiety regarding places from which escape might be difficult. It can be the most disabling of the phobias because it can significantly interfere with a person’s ability to function in work and social situations outside the home. In the United States, most researchers of panic disorder believe that agoraphobia almost always develops as a complication in patients with panic disorder. That is, the fear of having a panic attack in a public place from which escape would be formidable is thought to cause the agoraphobia. Although agoraphobia often coexists with panic disorder, DSM-5 classifies agoraphobia as a separate condition that may or may not be comorbid with panic disorder. HISTORY The term agoraphobia was coined in 1871 to describe the condition of patients who were afraid to venture alone into public places. The term is derived from the Greek words agora and phobos, meaning “fear of the marketplace.” EPIDEMIOLOGY The lifetime prevalence of agoraphobia is somewhat controversial, varying between 2 to 6 percent across studies. According to the DSM-5, persons older than age 65 years have a 0.4 percent prevalence rate of agoraphobia, but this may be a low estimate. The major factor leading to this wide range of estimates relates to disagreement about the conceptualization of agoraphobia’s relationship to panic disorder. Although studies of agoraphobia in psychiatric settings have reported that at least three fourths of the affected patients have panic disorder as well, studies of agoraphobia in community samples have found that as many as half the patients have agoraphobia without panic disorder. The reasons for these divergent findings are unknown but probably involve differences in ascertainment techniques. In many cases, the onset of agoraphobia follows a traumatic event. DIAGNOSIS AND CLINICAL FEATURES The DSM-5 diagnostic criteria for agoraphobia stipulates marked fear or anxiety about at least one situation from two or more of five situation groups: (1) using public transportation (e.g., bus, train, cars, planes), (2) in an open space (e.g., park, shopping center, parking lot), (3) in an enclosed space (e.g., stores, elevators, theaters), (4) in a crowd or standing in line, or (5) alone outside of the home. The fear or anxiety must be persistent and last at least 6 months (Table 9.3-1). Table 9.3-1 DSM-5 Diagnostic Criteria for Agoraphobia

Patients with agoraphobia rigidly avoid situations in which it would be difficult to obtain help. They prefer to be accompanied by a friend or a family member in busy streets, crowded stores, closed-in spaces (e.g., tunnels, bridges, and elevators), and closed-in vehicles (e.g., subways, buses, and airplanes). Patients may insist that they be accompanied every time they leave the house. The behavior can result in marital

discord, which may be misdiagnosed as the primary problem. Severely affected patients may simply refuse to leave the house. Particularly before a correct diagnosis is made, patients may be terrified that they are going crazy. Mrs. W was a 33-year-old married woman. She visited an

anxiety clinic reporting that she felt like she was having a heart attack whenever she left her home. Her disorder began 8 years earlier while attending a yoga class when she suddenly noticed a dramatic increase in her heartbeat, felt stabbing pains in her chest, and had difficulty breathing. She began sweating and trembling and felt dizzy. She immediately went to the emergency department, where an electrocardiogram was performed. No abnormalities were detected. Over the next few months, Mrs. W experienced similar attacks of 15 to 30 minutes' duration about four times per month. She often sought medical advice after each episode, and each time no physical abnormalities were detected. After experiencing a few of these attacks, Mrs. W became afraid of having an attack away from home and would not leave her home unless absolutely necessary, in which case she needed to have her cell phone or be accompanied by someone. Even so, she avoided crowded places such as malls, movie theaters, and banks, where rapid escape is sometimes blocked. Her symptoms and avoidance dominated her life, although she was aware that they were irrational and excessive. She experienced mild depression and restlessness and had difficulty sleeping. DIFFERENTIAL DIAGNOSIS The differential diagnosis for agoraphobia includes all the medical disorders that can cause anxiety or depression. The psychiatric differential diagnosis includes major depressive disorder, schizophrenia, paranoid personality disorder, avoidance personality disorder, and dependent personality disorder. COURSE AND PROGNOSIS Most cases of agoraphobia are thought to be caused by panic disorder. When the panic disorder is treated, the agoraphobia often improves with time. For rapid and complete reduction of agoraphobia, behavior therapy is sometimes indicated. Agoraphobia without a history of panic disorder is often incapacitating and chronic, and depressive disorders and alcohol dependence often complicate its course. TREATMENT Pharmacotherapy Benzodiazepines. Benzodiazepines have the most rapid onset of action against

panic. Some patients use them as needed when faced with a phobic stimulus. Alprazolam (Xanax) and lorazepam (Ativan) are the most commonly prescribed benzodiazepines. Clonazepam (Klonopin) has also been shown to be effective. The major reservations among clinicians regarding the use of benzodiazepines are the potential for dependence, cognitive impairment, and abuse, particularly with long-term use. However, when used appropriately under medical supervision, benzodiazepines are efficacious and generally well tolerated. The most common side effects are mild dizziness and sedation, both of which are generally attenuated by time or change of dose. Caution must be exercised when using heavy or dangerous machinery or when driving, especially when first starting the medication or when the dose is changed. Benzodiazepines should not be used in combination with alcohol because they can intensify its effects. Benzodiazepines are also best avoided in individuals with histories of alcohol or substance abuse unless there are compelling reasons, such as failure to respond to other classes of medications. Selective Serotonin Reuptake Inhibitors. SSRIs have been shown to help reduce or prevent relapse from various forms of anxiety, including agoraphobia. Effective doses are essentially the same as for the treatment of depression, although it is customary to start with lower initial doses than in depression to minimize an initial anxiolytic effect, which is almost always short lived, and to titrate upward somewhat slower toward a therapeutic dose. The main advantages of SSRIs antidepressants include their improved safety profile in overdose and more tolerable side-effect burden. Common side effects of most SSRIs are sleep disturbance, drowsiness, lightheadedness, nausea, and diarrhea; many of these adverse effects improve with continued use. Another commonly reported side effect of SSRIs is sexual dysfunction (i.e., decreased libido, delayed ejaculation in men, delayed orgasm in women), which rarely improves with time or switching among SSRIs (or from an SSRI to a serotonin-norepinephrine

reuptake inhibitor [SNRI]). Proposed strategies to combat sexual dysfunction in patients taking SSRIs include adjunctive use of yohimbine (Yocon), bupropion (Wellbutrin), or mirtazapine (Remeron); dose reduction; or adjunctive use of sildenafil (Viagra). Another issue to be considered when prescribing an SSRI is the possibility of a discontinuation syndrome if these medications are stopped abruptly. Commonly reported symptoms of this condition, which tend to occur 2 to 4 days after medication cessation, include increased anxiety, irritability, tearfulness, dizziness or lightheadedness, malaise, sleep disturbance, and concentration difficulties. This discontinuation syndrome is most common among SSRIs with shorter half-lives (e.g., paroxetine [Paxil]). Tricyclic and Tetracyclic Drugs. Although SSRIs are considered the first-line agents for treatment of panic disorders with or without agoraphobia, the tricyclic drugs clomipramine (Anafranil) and imipramine (Tofranil) are the most effective in the treatment of these disorders. Dosages must be titrated slowly upward to avoid overstimulation (e.g., “jitteriness” syndrome), and the full clinical benefit requires full dosages and may not be achieved for 8 to 12 weeks. Therapeutic drug monitoring

(TDM) may be useful to ensure that the patient is on an adequate dose of medication while avoiding issues of toxicity. The other adverse effects to these antidepressants are related to their effects on seizure threshold, as well as anticholinergic and potentially harmful cardiac effects, particularly in overdose. Psychotherapy Supportive Psychotherapy. Supportive psychotherapy involves the use of psychodynamic concepts and a therapeutic alliance to promote adaptive coping. Adaptive defenses are encouraged and strengthened, and maladaptive ones are discouraged. The therapist assists in reality testing and may offer advice regarding behavior. Insight-Oriented Psychotherapy. In insight-oriented psychotherapy, the goal is to increase the patient’s development of insight into psychological conflicts that, if unresolved, can manifest as symptomatic behavior. Behavior Therapy. In behavior therapy, the basic assumption is that change can occur without the development of psychological insight into underlying causes. Techniques include positive and negative reinforcement, systematic desensitization, flooding, implosion, graded exposure, response prevention, stop thought, relaxation techniques, panic control therapy, self-monitoring, and hypnosis. Cognitive Therapy. This is based on the premise that maladaptive behavior is secondary to distortions in how people perceive themselves and in how other perceive them. Treatment is short term and interactive, with assigned homework and tasks to be performed between sessions that focus on correcting distorted assumptions and cognitions. The emphasis is on confronting and examining situations that elicit interpersonal anxiety and associated mild depression. Virtual Therapy. Computer programs have been developed that allow patients to see themselves as avatars who are then placed in open or crowded spaces (e.g., a supermarket). As they identify with the avatars in repeated computer sessions, they are able to master their anxiety through deconditioning. REFERENCES Chambless DL, Sharpless BA, Rodriguez D, McCarthy KS, Milrod BL, Khalsa SR, Barber JP. Psychometric properties of the mobility inventory for agoraphobia: Convergent, discriminant, and criterion-related validity. Behav Therapy. 2011;42:689. Croft A, Hackmann A. Agoraphobia: An outreach treatment programme. Behav Cogn Psychother. 2013;41:359. Huppert JD, Kivity Y, Barlow DH, Gorman JM, Shear MK, Woods SW. Therapist effects and the outcome–alliance correlation in cognitive behavioral therapy for panic disorder with agoraphobia. Behav Res Ther. 2014;52:26–34. McCabe RE, Gifford S. Psychological treatment of panic disorder and agoraphobia. In: Anthony MM, Stein MB, eds. Oxford

# 04 - 9.4 Specific Phobia

# 9.4 Specific Phobia

Handbook of Anxiety and Related Disorders. New York: Oxford University Press; 2009:308. McClure-Tone EB, Pine DS. Clinical features of the anxiety disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1844. Meyerbroker K, Morina N, Kerkhof G, Emmelkamp PM. Virtual reality exposure treatment of agoraphobia: a comparison of computer automatic virtual environment and head-mounted display. Stud Health Technol Inform. 2011;167:51. Nay W, Brown R, Roberson-Nay R. Longitudinal course of panic disorder with and without agoraphobia using the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Psych Res. 2013;208:54. Perna G, Daccò S, Menotti R, Caldirola D. Antianxiety medications for the treatment of complex agoraphobia: Pharmacological interventions for a behavioral condition. Neuropsychiatr Dis Treat. 2011;7:621. Pollack MH, Simon NM. Pharmacotherapy for panic disorder and agoraphobia. In: Anthony MM, Stein MB, eds. Oxford Handbook of Anxiety and Related Disorders. New York: Oxford University Press; 2009:295. Ritchie K, Norton J, Mann A, Carriere I, Ancelin M-L. Late-onset agoraphobia: General population incidence and evidence for clinical subtype. Am J Psych. 2013;170:790. Vögele C, Ehlers A, Meyer AH, Frank M, Hahlweg K, Margraf J. Cognitive mediation of clinical improvement after intensive exposure therapy of agoraphobia and social phobia. Depress Anxiety. 2010;27:294. Wittchen HU, Gloster AT, Beesdo-Baum K, Fava GA, Craske MG. Agoraphobia: A review of the diagnostic classificatory position and criteria. Depress Anxiety. 2010;27:113. 9.4 Specific Phobia The term phobia refers to an excessive fear of a specific object, circumstance, or situation. A specific phobia is a strong, persisting fear of an object or situation. The diagnosis of specific phobia requires the development of intense anxiety, even to the point of panic, when exposed to the feared object. Persons with specific phobias may anticipate harm, such as being bitten by a dog, or may panic at the thought of losing control; for instance, if they fear being in an elevator, they may also worry about fainting after the door closes. EPIDEMIOLOGY Phobias are one of the most common mental disorders in the United States, where approximately 5 to 10 percent of the population is estimated to have these troubling and sometimes disabling disorders. The lifetime prevalence of specific phobia is about 10 percent. Specific phobia is the most common mental disorder among women and the second most common among men, second only to substance-related disorders. The 6month prevalence of specific phobia is about 5 to 10 per 100 persons (Table 9.4-1). The rates of specific phobias in women (14 to 16 percent) were double those of men (5 to 7 percent), although the ratio is closer to 1 to 1 for the fear of blood, injection, or injury type. (Types of phobias are discussed below in this section.) The peak age of onset for the natural environment type and the blood-injection-injury type is in the range of 5 to 9 years, although onset also occurs at older ages. In contrast, the peak age of onset for the situational type (except fear of heights) is higher, in the mid-20s, which is closer to the age of onset for agoraphobia. The feared objects and situations in specific phobias

(listed in descending frequency of appearance) are animals, storms, heights, illness, injury, and death. Table 9.4-1 Lifetime Prevalence Rates of Specific Phobia COMORBIDITY Reports of comorbidity in specific phobia range from 50 to 80 percent. Common comorbid disorders with specific phobia include anxiety, mood, and substance-related disorders. ETIOLOGY General Principles of Phobias Behavioral Factors. In 1920, John B. Watson wrote an article called "Conditioned Emotional Reactions," in which he recounted his experiences with Little Albert, an infant with a fear of rats and rabbits. Unlike Sigmund Freud's case of Little Hans, who had phobic symptoms (of horses) in the natural course of his maturation, Little Albert's difficulties were the direct result of the scientific experiments of two psychologists who used techniques that had successfully induced conditioned responses in laboratory animals. Watson's hypothesis invoked the traditional pavlovian stimulus–response model of the conditioned reflex to account for the creation of the phobia: Anxiety is aroused by a naturally frightening stimulus that occurs in contiguity with a second inherently neutral stimulus. As a result of the contiguity, especially when the two stimuli are paired on several successive occasions, the originally neutral stimulus becomes capable of arousing anxiety by itself. The neutral stimulus, therefore, becomes a conditioned stimulus for anxiety production. In the classic stimulus–response theory, the conditioned stimulus gradually loses its

potency to arouse a response if it is not reinforced by periodic repetition of the unconditioned stimulus. In phobias, attenuation of the response to the stimulus does not occur; the symptom may last for years without any apparent external reinforcement. Operant conditioning theory provides a model to explain this phenomenon: Anxiety is a drive that motivates the organism to do whatever it can to obviate a painful affect. In the course of its random behavior, the organism learns that certain actions enable it to avoid the anxiety-provoking stimulus. These avoidance patterns remain stable for long periods as a result of the reinforcement they receive from their capacity to diminish anxiety. This model is readily applicable to phobias in that avoidance of the anxietyprovoking object or situation plays a central part. Such avoidance behavior becomes fixed as a stable symptom because of its effectiveness in protecting the person from the phobic anxiety. Learning theory, which is particularly relevant to phobias, provides simple and intelligible explanations for many aspects of phobic symptoms. Critics contend, however, that learning theory deals mostly with surface mechanisms of symptom formation and is less useful than psychoanalytic theories in clarifying some of the complex underlying psychic processes involved. Psychoanalytic Factors. Sigmund Freud's formulation of phobic neurosis is still the analytic explanation of specific phobia and social phobia. Freud hypothesized that the major function of anxiety is to signal the ego that a forbidden unconscious drive is pushing for conscious expression and to alert the ego to strengthen and marshal its defenses against the threatening instinctual force. Freud viewed the phobia—anxiety hysteria, as he continued to call it—as a result of conflicts centered on an unresolved childhood oedipal situation. Because sex drives continue to have a strong incestuous coloring in adults, sexual arousal can kindle an anxiety that is characteristically a fear of castration. When repression fails to be entirely successful, the ego must call on auxiliary defenses. In patients with phobias, the primary defense involved is displacement; that is, the sexual conflict is displaced from the person who evokes the conflict to a seemingly unimportant, irrelevant object or situation, which then has the power to arouse a constellation of affects, one of which is called signal anxiety. The phobic object or situation may have a direct associative connection with the primary source of the conflict and thus symbolizes it (the defense mechanism of symbolization). Furthermore, the situation or the object is usually one that the person can avoid; with the additional defense

mechanism of avoidance, the person can escape suffering serious anxiety. The end result is that the three combined defenses (repression, displacement, and symbolization) may eliminate the anxiety. The anxiety is controlled at the cost of creating a phobic neurosis, however. Freud first discussed the theoretical formulation of phobia formation in his famous case history of Little Hans, a 5-year-old boy who feared horses. Although psychiatrists followed Freud's thought that phobias resulted from castration anxiety, recent psychoanalytic theorists have suggested that other types of anxiety may be involved. In agoraphobia, for example, separation anxiety clearly plays a leading

role, and in erythrophobia (a fear of red that can be manifested as a fear of blushing), the element of shame implies the involvement of superego anxiety. Clinical observations have led to the view that anxiety associated with phobias has a variety of sources and colorings. Phobias illustrate the interaction between a genetic constitutional diathesis and environmental stressors. Longitudinal studies suggest that certain children are constitutionally predisposed to phobias because they are born with a specific temperament known as behavioral inhibition to the unfamiliar, but a chronic environmental stress must act on a child's temperamental disposition to create a fullblown phobia. Stressors, such as the death of a parent, separation from a parent, criticism or humiliation by an older sibling, and violence in the household, may activate the latent diathesis within the child, who then becomes symptomatic. An overview of psychodynamic aspects of phobias is summarized in Table 9.4-2. Table 9.4-2 Psychodynamic Themes in Phobias COUNTERPHOBIC ATTITUDE. Otto Fenichel called attention to the fact that phobic anxiety can be hidden behind attitudes and behavior patterns that represent a denial, either that the dreaded object or situation is dangerous or that the person is afraid of it. Instead of being a passive victim of external circumstances, a person reverses the situation and actively attempts to confront and master whatever is feared. Persons with counterphobic attitudes seek out situations of danger and rush enthusiastically toward them. Devotees of potentially dangerous sports, such as parachute jumping and rock climbing, may be exhibiting counterphobic behavior. Such patterns may be secondary to phobic anxiety or may be normal means of dealing with a realistically dangerous situation. Children's play may exhibit counterphobic elements, as when children play doctor and give a doll the shot they received earlier that day in the pediatrician's office. This pattern of behavior may involve the related defense mechanism of identifying with the aggressor.

Specific Phobia The development of specific phobia may result from the pairing of a specific object or situation with the emotions of fear and panic. Various mechanisms for the pairing have been postulated. In general, a nonspecific tendency to experience fear or anxiety forms the backdrop; when a specific event (e.g., driving) is paired with an emotional experience (e.g., an accident), the person is susceptible to a permanent emotional association between driving or cars and fear or anxiety. The emotional experience itself can be in response to an external incident, as a traffic accident, or to an internal incident, most commonly a panic attack. Although a person may never again experience a panic attack and may not meet the diagnostic criteria for panic disorder, he or she may have a generalized fear of driving, not an expressed fear of having a panic attack while driving. Other mechanisms of association between the phobic object and the phobic emotions include modeling, in which a person observes the reaction in another (e.g., a parent), and information transfer, in which a person is taught or warned about the dangers of specific objects (e.g., venomous snakes). Genetic Factors. Specific phobia tends to run in families. The blood-injectioninjury type has a particularly high familial tendency. Studies have reported that twothirds to three-fourths of affected probands have at least one first-degree relative with specific phobia of

the same type, but the necessary twin and adoption studies have not been conducted to rule out a significant contribution by nongenetic transmission of specific phobia. DIAGNOSIS The DSM-5 includes distinctive types of specific phobia: animal type, natural environment type (e.g., storms), blood-injection-injury type (e.g., needles), situational type (e.g., cars, elevators, planes), and other type (for specific phobias that do not fit into the previous four types). The key feature of each type of phobia is that fear symptoms occur only in the presence of a specific object (Table 9.4-3). The bloodinjection-injury type is differentiated from the others in that bradycardia and hypotension often follow the initial tachycardia that is common to all phobias. The blood-injection-injury type of specific phobia is particularly likely to affect many members and generations of a family. One type of phobia of recently reported phobia is space phobia, in which persons fear falling when there is no nearby support, such as a wall or a chair. Some data indicate that affected persons may have abnormal right hemisphere function, possibly resulting in visual-spatial impairment. Balance disorders should be ruled out in such patients. Table 9.4-3 DSM-5 Diagnostic Criteria for Specific Phobia

Phobias have traditionally been classified according to specific fear by means of Greek or Latin prefixes, as indicated in Table 9.4-4. Other phobias that are related to changes in the society are the fear of electromagnetic fields, of microwaves, and of society as a

whole (amaxophobia). Table 9.4-4 Phobias Mr. S was a successful lawyer who presented for treatment after his firm, to which he had previously been able to walk from home, moved to a new location that he could only reach by driving. Mr. S reported that he was “terrified” of driving, particularly on highways. Even the thought of getting into a car led him to worry that he would die in a fiery crash. His thoughts were associated with intense fear and numerous somatic symptoms, including a racing heart, nausea, and sweating. Although the thought of driving was terrifying in and of itself, Mr. S became nearly incapacitated when he drove on busy roads, often having to pull over to vomit. (Courtesy of Erin B. McClure-Tone, Ph.D., and Daniel S. Pine, M.D.) CLINICAL FEATURES Phobias are characterized by the arousal of severe anxiety when patients are exposed to specific situations or objects or when patients even anticipate exposure to the situations or objects. Exposure to the phobic stimulus or anticipation of it almost invariably results in a panic attack in a person who is susceptible to them. Persons with phobias, by definition, try to avoid the phobic stimulus; some go to great trouble to avoid anxiety-provoking situations. For example, a patient with a phobia may take a bus across the United States, rather than fly, to avoid contact with the object of the patient’s phobia, an airplane. Perhaps as another way to avoid the stress of the phobic stimulus, many patients have substance-related disorders, particularly alcohol use disorders. Moreover, an estimated one-third of patients with social phobia have major depressive disorder. The major finding on the mental status examination is the presence of an irrational and ego-dystonic fear of a specific situation, activity, or object; patients are able to describe how they avoid contact with the phobia. Depression is commonly found on the mental status examination and may be present in as many as one-third of all patients

with phobia. Differential Diagnosis Nonpsychiatric medical conditions that can result in the development of a phobia include the use of substances (particularly hallucinogens and sympathomimetics), CNS tumors, and cerebrovascular diseases. Phobic symptoms in these instances are unlikely in the absence of additional suggestive findings on physical, neurological, and mental status examinations. Schizophrenia is also in the differential diagnosis of specific

phobia because patients with schizophrenia can have phobic symptoms as part of their psychoses. Unlike patients with schizophrenia, however, patients with phobia have insight into the irrationality of their fears and lack the bizarre quality and other psychotic symptoms that accompany schizophrenia. In the differential diagnosis of specific phobia, clinicians must consider panic disorder, agoraphobia, and avoidant personality disorder. Differentiation among panic disorder, agoraphobia, social phobia, and specific phobia can be difficult in individual cases. In general, however, patients with specific phobia tend to experience anxiety immediately when presented with the phobic stimulus. Furthermore, the anxiety or panic is limited to the identified situation; patients are not abnormally anxious when they are neither confronted with the phobic stimulus nor caused to anticipate the stimulus. Other diagnoses to consider in the differential diagnosis of specific phobia are hypochondriasis, OCD, and paranoid personality disorder. Whereas hypochondriasis is the fear of having a disease, specific phobia of the illness type is the fear of contracting the disease. Some patients with OCD manifest behavior indistinguishable from that of a patient with specific phobia. For example, whereas patients with OCD may avoid knives because they have compulsive thoughts about killing their children, patients with specific phobia about knives may avoid them for fear of cutting themselves. Patients with paranoid personality disorder have generalized fear that distinguishes them from those with specific phobia. COURSE AND PROGNOSIS Specific phobia exhibits a bimodal age of onset, with a childhood peak for animal phobia, natural environment phobia, and blood-injection-injury phobia and an early adulthood peak for other phobias, such as situational phobia. Limited prospective epidemiological data are available that chart the natural course of specific phobia. Because patients with isolated specific phobia rarely present for treatment, there is also little research on the course of the disorder in the clinic. The limited information that is available suggests that most specific phobias that begin in childhood and persist into adulthood will continue to persist for many years. The severity of the condition is believed to remain relatively constant, which contrasts with the waxing and waning course seen in other anxiety disorders.

TREATMENT Phobias Behavior Therapy. The most studied and most effective treatment for phobias is probably behavior therapy. The key aspects of successful treatment are (1) the patient’s commitment to treatment; (2) clearly identified problems and objectives; and (3) available alternative strategies for coping with the feelings. A variety of behavioral treatment techniques have been used, the most common being systematic desensitization, a method pioneered by Joseph Wolpe. In this method, the patient is exposed serially to a predetermined list of anxiety-provoking stimuli graded in a hierarchy from the least to the most frightening. Through the use of antianxiety drugs, hypnosis, and instruction in muscle relaxation, patients are taught how to induce in themselves both mental and physical repose. After they have mastered the techniques, patients are taught to use them to induce relaxation in the face of each anxietyprovoking stimulus. As they become desensitized to each stimulus in the scale, the patients move up to the next stimulus until, ultimately, what previously produced the most anxiety no longer elicits the painful affect. Other behavioral techniques that have been used more recently involve intensive exposure to the phobic stimulus through either imagery or desensitization in vivo. In imaginal flooding, patients are exposed to the phobic stimulus for as long as they can tolerate the fear until they reach a point at which they can no longer feel it. Flooding (also known as implosion) in vivo requires patients to experience similar anxiety through exposure to the actual phobic stimulus. Insight-Oriented Psychotherapy. Early in the development of psychoanalysis and the dynamically oriented psychotherapies, theorists believed that these methods were the treatments of choice for phobic

neurosis, which was then thought to stem from oedipal-genital conflicts. Soon, however, therapists recognized that, despite progress in uncovering and analyzing unconscious conflicts, patients frequently failed to lose their phobic symptoms. Moreover, by continuing to avoid phobic situations, patients excluded a significant degree of anxiety and its related associations from the analytic process. Both Freud and his pupil Sandor Ferenczi recognized that if progress in analyzing these symptoms was to be made, therapists had to go beyond their analytic roles and actively urge patients with phobia to seek the phobic situation and experience the anxiety and resultant insight. Since then, psychiatrists have generally agreed that a measure of activity on the therapist's part is often required to treat phobic anxiety successfully. The decision to apply the techniques of psychodynamic insight-oriented therapy should be based not on the presence of phobic symptoms alone but on positive indications from the patient's ego structure and life patterns for the use of this method of treatment. Insight-oriented therapy enables patients to understand the origin of the phobia, the phenomenon of secondary gain, and the role of resistance and enables them to seek

healthy ways of dealing with anxiety-provoking stimuli. Virtual Therapy. A number of computer-generated simulations of phobic disorders have been developed. Patients are exposed to or interact with the phobic object or situation on the computer screen. Countless numbers of such programs are available, and others are in continual development. Variable success rates have been reported, but virtual therapy for phobic disorder is on the cutting edge of using computers to treat mental illness. Other Therapeutic Modalities. Hypnosis, supportive therapy, and family therapy may be useful in the treatment of phobic disorders. Hypnosis is used to enhance the therapist's suggestion that the phobic object is not dangerous, and self-hypnosis can be taught to the patient as a method of relaxation when confronted with the phobic object. Supportive psychotherapy and family therapy are often useful in helping the patient actively confront the phobic object during treatment. Not only can family therapy enlist the aid of the family in treating the patient, but it may also help the family understand the nature of the patient's problem. Specific Phobia A common treatment for specific phobia is exposure therapy. In this method, therapists desensitize patients by using a series of gradual, self-paced exposures to the phobic stimuli, and they teach patients various techniques to deal with anxiety, including relaxation, breathing control, and cognitive approaches. The cognitive-behavioral approaches include reinforcing the realization that the phobic situation is, in fact, safe. The key aspects of successful behavior therapy are the patient's commitment to treatment, clearly identified problems and objectives, and alternative strategies for coping with the patient's feelings. In the special situation of blood-injection-injury phobia, some therapists recommend that patients tense their bodies and remain seated during the exposure to help avoid the possibility of fainting from a vasovagal reaction to the phobic stimulation. β-adrenergic receptor antagonists may be useful in the treatment of specific phobia, especially when the phobia is associated with panic attacks. Pharmacotherapy (e.g., benzodiazepines), psychotherapy, or combined therapy directed to the attacks may also be of benefit. REFERENCES Britton JC, Gold AL, Deckersbach T, Rauch SL. Functional MRI study of specific animal phobia using an event-related emotional counting stroop paradigm. Depress Anxiety. 2009;26:796. Coelho CM, Purkis H. The origins of specific phobias: Influential theories and current perspectives. Rev Gen Psychology. 2009;13:335. Gamble AL, Harvey AG, Rapee RM. Specific phobia. In: Stein DJ, Hollander E, Rothbaum BO, eds. Textbook of Anxiety Disorders. 2nd Edition. Arlington, VA: American Psychiatric Publishing; 2009:525. Hamm AO. Specific phobias. Psychiatr Clin North Am. 2009;32(3):577.

# 05 - 9.5 Social Anxiety Disorder (Social Phobia)

# 9.5 Social Anxiety Disorder (Social Phobia)

Ipser JC, Singh L, Stein DJ. Meta-analysis of functional brain imaging in specific phobia. Psych Clin Neurosci. 2013;67:311. Lipka J, Miltner WR, Straube T. Vigilance for threat interacts with amygdala responses to subliminal threat cues in specific phobia. Biol Psychiatry. 2011;70:472. McClure-Tone EB, Pine DS. Clinical features of the anxiety disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009;1844. McTeague LM, Lang PJ, Wangelin BC, Laplante MC, Bradley MM. Defensive mobilization in specific phobia: Fear specificity, negative affectivity, and diagnostic prominence. Biol Psychiatry. 2012;72:8. Podina˘a IR, Kosterb EHW, Philippotc P, Dethierc V, David DO. Optimal attentional focus during exposure in specific phobia: A meta-analysis. Clin Psychol Rev. 2013;33:1172. Price K, Veale D, Brewin CR. Intrusive imagery in people with a specific phobia of vomiting. J Behav Ther Exp Psychiatry. 2012;43:672. Salas MM, Brooks AJ, Rowe JE. The immediate effect of a brief energy psychology intervention (Emotional Freedom Techniques) on specific phobias: A pilot study. Exposure. 2011;7:155. Simos G, Hofmann SG, Öst L-G, Reuterskiöld L. Specific phobias. In: Simos G, Hofmann SG, eds. CBT For Anxiety Disorders: A Practitioner Book. Malden, MA: Wiley-Blackwell;2013:107. Trumpf J, Margraf J, Vriends N, Meyer AH, Becker ES. Predictors of specific phobia in young women: A prospective community study. J Anxiety Disord. 2010;24:87. Van Houtm C, Laine M, BoomsmA D, Ligthart L, van Wijk A, De Jongh A. A review and meta-analysis of the heritability of specific phobia subtypes and corresponding fears. J Anxiety Disord. 2013;27:379. Waters AM, Bradley BP, Mogg K. Biased attention to threat in paediatric anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder) as a function of 'distress' versus 'fear' diagnostic categorization. Psychol Med. 2014;1–10. Zimmerman M, Dalrymple K, Chelminski I, Young D, Galione JN. Recognition of irrationality of fear and the diagnosis of social anxiety disorder and specific phobia in adults: Implications for criteria revision in DSM-5. Depress Anxiety. 2010;27:1044. 9.5 Social Anxiety Disorder (Social Phobia) Social anxiety disorder (also referred to as social phobia) involves the fear of social situations, including situations that involve scrutiny or contact with strangers. The term social anxiety reflects the distinct differentiation of social anxiety disorder from specific phobia, which is the intense and persistent fear of an object or situation. Persons with social anxiety disorder are fearful of embarrassing themselves in social situations (i.e., social gatherings, oral presentations, meeting

new people). They may have specific fears about performing specific activities such as eating or speaking in front of others, or they may experience a vague, nonspecific fear of “embarrassing oneself.” In either case, the fear in social anxiety disorder is of the embarrassment that may occur in the situation, not of the situation itself. EPIDEMIOLOGY Various studies have reported a lifetime prevalence ranging from 3 to 13 percent for social anxiety disorder. The 6-month prevalence is about 2 to 3 per 100 persons (Table

9.5-1). In epidemiological studies, females are affected more often than males, but in clinical samples, the reverse is often true. The reasons for these varying observations are unknown. The peak age of onset for social anxiety disorder is in the teens, although onset is common as young as 5 years of age and as old as 35 years. Table 9.5-1 Lifetime Prevalence Rates of Social Anxiety Disorder COMORBIDITY Persons with social anxiety disorder may have a history of other anxiety disorders, mood disorders, substance-related disorders, and bulimia nervosa. ETIOLOGY Several studies have reported that some children possibly have a trait characterized by a consistent pattern of behavioral inhibition. This trait may be particularly common in the children of parents who are affected with panic disorder, and it may develop into severe shyness as the children grow older. At least some persons with social anxiety disorder may have exhibited behavioral inhibition during childhood. Perhaps associated with this trait, which is thought to be biologically based, are the psychologically based data indicating that the parents of persons with social anxiety disorder, as a group, were less caring, more rejecting, and more overprotective of their children than were other parents. Some social anxiety disorder research has referred to the spectrum from dominance to submission observed in the animal kingdom. For example, whereas dominant humans may tend to walk with their chins in the air and to make eye contact, submissive humans may tend to walk with their chins down and to avoid eye contact. Neurochemical Factors

The success of pharmacotherapies in treating social anxiety disorder has generated two specific neurochemical hypotheses about two types of social anxiety disorder. Specifically, the use of β-adrenergic receptor antagonists—for example, propranolol (Inderal)—for performance phobias (e.g., public speaking) has led to the development of an adrenergic theory for these phobias. Patients with performance phobias may release more norepinephrine or epinephrine, both centrally and peripherally, than do nonphobic persons, or such patients may be sensitive to a normal level of adrenergic stimulation. The observation that MAOIs may be more effective than tricyclic drugs in the treatment of generalized social anxiety disorder, in combination with preclinical data, has led some investigators to hypothesize that dopaminergic activity is related to the pathogenesis of the disorder. One study has shown significantly lower homovanillic acid concentrations. Another study using SPECT demonstrated decreased striatal dopamine reuptake site density. Thus, some evidence suggests dopaminergic dysfunction in social anxiety disorder. Genetic Factors First-degree relatives of persons with social anxiety disorder are about three times more likely to be affected with social anxiety disorder than are first-degree relatives of those without mental disorders. And some preliminary data indicate that monozygotic twins are more often concordant than are dizygotic twins, although in social anxiety disorder, it is particularly important to study twins reared apart to help control for environmental factors. DIAGNOSIS AND CLINICAL FEATURES The DSM-5 diagnostic criteria for social anxiety disorder is listed in Table 9.5-2. The clinician should recognize that at least some degree of social anxiety or selfconsciousness is common in the general population. Community studies suggest that roughly one-third of all persons consider themselves to be far more anxious than other people in social situations. Moreover, such concerns

may appear particularly heightened during certain developmental stages, such as adolescence, or after life transitions, such as marriage or occupation changes, associated with new demands for social interaction. Such anxiety only becomes social anxiety disorder when the anxiety either prevents an individual from participating in desired activities or causes marked distress during such activities. DSM-5 also includes a performance only diagnostic specifier for persons who have extreme social phobia specifically about speaking or performing in public. Table 9.5-2 DSM-5 Diagnostic Criteria for Social Anxiety Disorder

Ms. B was a 29-year-old computer programmer who presented for treatment after she was offered promotion to a managerial position at her firm. Although she wanted the raise and the increased responsibility that would come with the new job, which she had agreed to try on a probationary basis, Ms. B reported that she was reluctant to accept the position because it required frequent interactions with employees from other divisions of the company, as well as occasional public speaking. She stated that she had always felt nervous around new people, whom she worried would ridicule her

for “saying stupid things” or committing social faux pas. She also reported feeling “terrified” to speak before groups. These fears had not previously interfered with her social life and job performance. However, since starting her probationary job, Ms. B reported that they had become problematic. She noted that when she had to interact with others, her heart started racing, her mouth became dry, and she felt sweaty. At meetings, she had sudden thoughts that she would say something very foolish or commit a terrible social gaffe that would cause people to laugh. As a consequence, she had skipped several important meetings and left others early. (Courtesy of Erin B. McClure-Tone, Ph.D., and Daniel S. Pine, M.D.) DIFFERENTIAL DIAGNOSIS Social anxiety disorder needs to be differentiated from appropriate fear and normal shyness, respectively. Differential diagnostic considerations for social anxiety disorder are agoraphobia, panic disorder, avoidant personality disorder, major depressive disorder, and schizoid personality disorder. A patient with agoraphobia is often comforted by the presence of another person in an anxiety-provoking situation, but a patient with social anxiety disorder is made more anxious by the presence of other people. Whereas breathlessness, dizziness, a sense of suffocation, and a fear of dying are common in panic disorder and agoraphobia, the symptoms associated with social anxiety disorder usually involve blushing, muscle twitching, and anxiety about scrutiny. Differentiation between social anxiety disorder and avoidant personality disorder can be difficult and can require extensive interviews and psychiatric histories. The avoidance of social situations can often be a symptom in depression, but a psychiatric interview with the patient is likely to elicit a broad constellation of depressive symptoms. In patients with schizoid personality disorder, the lack of interest in socializing, not the fear of socializing, leads to the avoidant social behavior. COURSE AND PROGNOSIS Social anxiety disorder tends to have its onset in late childhood or early adolescence. Existing prospective epidemiological findings indicate that social anxiety disorder is typically chronic, although patients whose symptoms do remit tend to stay well. Both retrospective epidemiological studies and prospective clinical studies suggest that the disorder can profoundly disrupt the life of an individual over many years. This can include disruption in school or academic achievement and interference with job performance and social development. TREATMENT Both psychotherapy and pharmacotherapy are useful in treating social anxiety disorder. Some studies indicate that the use of both pharmacotherapy and psychotherapy produces better results than either therapy alone, although the finding may not be

applicable to all situations and patients. Effective drugs for the treatment of social anxiety disorder include (1) SSRIs, (2) the benzodiazepines, (3) venlafaxine (Effexor), and (4) buspirone (BuSpar). Most clinicians consider SSRIs the first-line treatment choice for patients with more generalized forms of social anxiety disorder. The benzodiazepines alprazolam (Xanax) and clonazepam (Klonopin) are also efficacious in social anxiety disorder. Buspirone has shown additive effects when used to augment treatment with SSRIs. In severe cases, successful treatment of social anxiety disorder with both irreversible MAOIs such as phenelzine (Nardil) and reversible inhibitors of monoamine oxidase such as moclobemide (Aurorix) and brofaromine (Consonar), which are not available in the United States, has been reported. Therapeutic dosages of phenelzine range from 45 to 90 mg a day, with response rates ranging from 50 to 70 percent; approximately 5 to 6 weeks is needed to assess the efficacy. The treatment of social anxiety disorder associated with performance situations frequently involves the use of β-adrenergic receptor antagonists shortly before exposure to a phobic stimulus. The two compounds most widely used are atenolol (Tenormin) 50 to 100 mg taken about 1 hour before the performance, or propranolol, 20 to 40 mg. Another option to help with performance anxiety is a relatively short- or intermediateacting benzodiazepine, such as lorazepam or alprazolam. Cognitive, behavioral, and exposure techniques are also useful in performance situations. Psychotherapy for social anxiety disorder usually involves a combination of behavioral and cognitive methods, including cognitive retraining, desensitization, rehearsal during sessions, and a range of homework assignments. REFERENCES Baillie AJ, Sannibale C, Stapinski LA, Teesson M, Rapee RM, Haber PS. An investigator-blinded, randomized study to compare the efficacy of combined CBT for alcohol use disorders and social anxiety disorder versus CBT focused on alcohol alone in adults with comorbid disorders: The Combined Alcohol Social Phobia (CASP) trial protocol. BMC Psychiatry. 2013;13:199. Blanco C, Schneier FR, Vesga-Lopez O, Liebowitz MR. Pharmacotherapy for social anxiety disorder. In: Stein DJ, Hollander E, Rothbaum BO, eds. Textbook of Anxiety Disorders. 2nd edition. Arlington, VA: American Psychiatric Publishing; 2009:471. Doehrmann O, Ghosh SS, Polli FE, Reynolds GO, Horn F, Keshavan A, Triantafyllou C, Saygin ZM, Whitfield-Gabrieli S, Hofmann SG, Pollack M, Gabriel JD. Treatment response in social anxiety disorder from functional magnetic resonance imaging. JAMA Psych. 2013;70:87. Essex MJ, Klein MH, Slattery MJ, Goldsmith HH, Kalin NH. Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. Am J Psychiatry. 2010;167:40. Goldin PR, Ziv M, Jazaieri H, Hahn K, Heimberg R, Gross JJ. Impact of cognitive behavioral therapy for social anxiety disorder on the neural dynamics of cognitive reappraisal of negative self-beliefs: Randomized clinical trial. JAMA. 2013;70:1048. Hofmann SG, Asnaani A, Hinton DE. Cultural aspects in social anxiety and social anxiety disorder. Depress Anxiety. 2010;27:1117.

# 06 - 9.6 Generalized Anxiety Disorder

# 9.6 Generalized Anxiety Disorder

Hofmann SG, DiBartolo PM. Social Anxiety: Clinical, Developmental, and Social Perspectives. 2nd edition. San Diego: Academic Press; 2010. Hofmann SG, Smits JAJ, Rosenfield D, Simon N, Otto MW, Meuret AE, Marques L, Fang A, Tart C, Pollack MH. DCycloserine as an augmentation strategy with cognitive-behavioral therapy for social anxiety disorder. Am J Psych. 2013;170:751. Leichsenring F, Salzer S, Beutel ME, Herpertz S. Psychodynamic therapy and cognitive-behavioral therapy in social anxiety disorder: A multicenter randomized controlled trial. Am J Psych. 2013;170:759. McClure-Tone EB, Pine DS. Clinical features of the anxiety disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1844. Morreale M, Tancer ME, Uhde TW. Pathogenesis of social anxiety disorder. In: Stein DJ, Hollander E, Rothbaum BO, eds. Textbook of Anxiety Disorders. 2nd edition. Arlington, VA: American Psychiatric Publishing; 2009:453. Penttinen H, Wahlström J. Progress in assimilation of problematic experience in group therapy for social phobia: A subgroup analysis. J Contemp Psychother. 2013;43:123. Pollack MH, Van Ameringen M, Simon NM, Worthington JW, Hoge EA, Keshaviah A, Stein, MB. A double-blind randomized controlled trial of augmentation and switch strategies for refractory social anxiety disorder. Am J Psychiatry. 2014; 171(1):44–53. Teo AR, Lerrigo R, Rogers MA. The role of social isolation in social anxiety disorder: A systematic review and metaanalysis. J Anxiety Disorders. 2013;27:353. Yuen EK, Herbert JD, Forman EM, Goetter EM, Juarascio AS, Rabin S, Goodwin C, Bouchard S. Acceptance based behavior therapy for social anxiety disorder through videoconferencing. J Anxiety Disorders. 2013;27:389. 9.6 Generalized Anxiety Disorder Anxiety can be conceptualized as a normal and adaptive response to threat that prepares the organism for flight or fight. Persons who seem to be anxious about almost everything, however, are likely to be classified as having generalized anxiety disorder. Generalized anxiety disorder is defined as excessive anxiety and worry about several events or activities for most days during at least a 6-month period. The worry is difficult to control and is associated with somatic symptoms, such as muscle tension, irritability, difficulty sleeping, and restlessness. The anxiety is not focused on features of another disorder, is not caused by substance use or a general medical condition, and does not occur only during a mood or psychiatric disorder. The anxiety is difficult to control, is subjectively distressing, and produces impairment in important areas of a person's life. EPIDEMIOLOGY Generalized anxiety disorder is a common condition; reasonable estimates for its 1-

year prevalence range from 3 to 8 percent. The ratio of women to men with the disorder is about 2 to 1, but the ratio of women to men who are receiving inpatient treatment for the disorder is about 1 to 1. A lifetime prevalence is close to 5 percent with the Epidemiological Catchment Area (ECA) study suggesting a lifetime prevalence as high as 8 percent. In anxiety disorder clinics, about 25 percent of patients have generalized

anxiety disorder. The disorder usually has its onset in late adolescence or early adulthood, although cases are commonly seen in older adults. Also, some evidence suggests that the prevalence of generalized anxiety disorder is particularly high in primary care settings. COMORBIDITY Generalized anxiety disorder is probably the disorder that most often coexists with another mental disorder, usually social phobia, specific phobia, panic disorder, or a depressive disorder. Perhaps 50 to 90 percent of patients with generalized anxiety disorder have another mental disorder. As many as 25 percent of patients eventually experience panic disorder. Generalized anxiety disorder is differentiated from panic disorder by the absence of spontaneous panic attacks. An additional high percentage of patients are likely to have major depressive disorder. Other common disorders associated with generalized anxiety disorder are dysthymic disorder and substancerelated disorders. ETIOLOGY The cause of generalized anxiety disorder is not known. As currently defined, generalized anxiety disorder probably affects a heterogeneous group of persons. Perhaps because a certain degree of anxiety is normal and adaptive, differentiating normal anxiety from pathological anxiety and differentiating biological causative factors from psychosocial factors are difficult. Biological and psychological factors probably work together. Biological Factors The therapeutic efficacies of benzodiazepines and the azaspirones (e.g., buspirone [BuSpar]) have focused biological research efforts on the γ-aminobutyric acid and serotonin neurotransmitter systems. Whereas benzodiazepines (which are benzodiazepine receptor agonists) are known to reduce anxiety, flumazenil (Romazicon) (a benzodiazepine receptor antagonist) and the β-carbolines (benzodiazepine receptor reverse agonists) are known to induce anxiety. Although no convincing data indicate that the benzodiazepine receptors are abnormal in patients with generalized anxiety disorder, some researchers have focused on the occipital lobe, which has the highest concentrations of benzodiazepine receptors in the brain. Other brain areas hypothesized to be involved in generalized anxiety disorder are the basal ganglia, the limbic system, and the frontal cortex. Because buspirone is an agonist at the serotonin 5-HT1A receptor, there is the hypothesis that the regulation of the serotonergic system in generalized anxiety disorder is abnormal. Other neurotransmitter systems that have been the subject of research in generalized anxiety disorder include the norepinephrine, glutamate, and cholecystokinin systems. Some evidence indicates that patients with generalized anxiety disorder may have subsensitivity of their α2-adrenergic receptors, as indicated by a

blunted release of growth hormone after clonidine (Catapres) infusion. Brain imaging studies of patients with generalized anxiety disorder have revealed significant findings. One PET study reported a lower metabolic rate in basal ganglia and white matter in patients with generalized anxiety disorder than in normal control subjects. A few genetic studies have also been conducted in the field. One study found that a genetic relation might exist between generalized anxiety disorder and major depressive disorder in women. Another study showed a distinct, but difficult-toquantitate, genetic component in generalized anxiety disorder. About 25 percent of firstdegree relatives of patients with generalized anxiety disorder are also affected. Male relatives are likely to have an alcohol use disorder. Some twin studies report a concordance rate of 50 percent in

monozygotic twins and 15 percent in dizygotic twins. Table 9.6-1 lists relative genetic risks in selected anxiety disorders. Table 9.6-1 Familial Relative Risks in Selected Anxiety Disorders A variety of electroencephalogram (EEG) abnormalities has been noted in alpha rhythm and evoked potentials. Sleep EEG studies have reported increased sleep discontinuity, decreased delta sleep, decreased stage 1 sleep, and reduced rapid eye movement sleep. These changes in sleep architecture differ from the changes seen in depressive disorders. Psychosocial Factors The two major schools of thought about psychosocial factors leading to the development of generalized anxiety disorder are the cognitive-behavioral school and the psychoanalytic school. According to the cognitive-behavioral school, patients with generalized anxiety disorder respond to incorrectly and inaccurately perceived dangers. The inaccuracy is generated by selective attention to negative details in the environment, by distortions in information processing, and by an overly negative view of the person's own ability to cope. The psychoanalytic school hypothesizes that anxiety is a symptom of unresolved, unconscious conflicts. Sigmund Freud first presented this psychological theory in 1909 with his description of Little Hans; before then, Freud had conceptualized anxiety as having a physiological basis. An example of Freudian theory as applied to general anxiety can be seen in the following case:

Mrs. B, a 26-year-old married woman, was admitted to the hospital for the evaluation of persistent anxiety that had begun 8 months earlier and was becoming increasingly disabling. Especially disturbing to the patient was the spontaneous intrusion of intermittent images in her mind's eye of her father and herself locked in a naked sexual embrace. The images were not only frightening, but they puzzled her greatly because she had always disliked her father intensely. Not only was he "poison" to her, but she tried to avoid any contact with him and found it difficult to talk to him if she was forced to be in his company. As the patient described the difficulty of her relationship with her father, she suddenly recalled that her anxiety had begun at a time when her father was seemingly being more intrusive than ever as he tried to help her and her husband over a period of financial difficulty. As the patient continued to revile her father, she suddenly commented that her mother had told her that her father "had been good to me when I was little and he used to sing songs to me and take me on his lap, but I don't remember. I only remember when he was mean to me. I just am glad when he keeps on talking mean to me the way he always has. I just wouldn't know what to do if he was nice to me." When asked by the interviewer if there might have been a time when she had wanted him to be nice to her, the patient replied, "When I was little, I just wanted to know that he did love me a little. I guess I always wanted him to be nice to me. But when I stop to think about it, I guess I didn't want him to be nice to me." The doctor then commented, "It sounds as if a part of you wants to be close to your father." In response, the patient burst into agitated sobs and blurted out, "I don't know how to be close to my father! I am too old to care about my father now!" When the patient regained her composure, she recalled the memory of an event she had not thought of since it had occurred 15 years earlier. When she was 11 years old, she reported, while in the living room with her father, she had suddenly had the mental image of being in a sexual embrace with him. Terrified, she had run into the kitchen to find her mother. There had been no recurrence of that image until the onset of the current illness, and the incident had remained forgotten until its recall during the interview. Its emergence into consciousness amplified the history of the patient's illness and disclosed an earlier transient outbreak of the same symptoms she had experienced as an adult. After the patient had recovered her composure, she recalled further hitherto forgotten memories. She had slept in her parents' bedroom until she was 6, during which period her father, on one occasion, had taken her into bed

and told her stories and, on another, had yelled at her very angrily as she lay in her crib. During a clinical interview the next day, the patient revealed a fact that she had forgotten in her earlier account of her illness: At the end of the period during which her father had been making the friendly overtures that had so deeply troubled her, and the night before the sudden onset of her symptoms, she had had a nightmare. She was, she dreamed, at a zoo. It was night, and she heard strange noises in the darkness. She asked an attendant standing next to her what the noises were. “Oh,” the

attendant replied casually, “that’s only the animals mating.” She then noticed a large, gray elephant lying on its right side in the grass in front of her. As she watched, she noticed the creature moving its left hind leg up and down as if it were trying to get to its feet. At that point she awoke from the dream with a feeling of terror and, afterward, during the morning, experienced the first episode of the frightening imagery of sexual activity with her father. In direct association to the dream, the patient recalled a long-forgotten childhood memory of an incident that had occurred during her fourth or fifth year. She had awoken one night while in her crib in her parents’ bedroom to observe her parents having sexual intercourse. They suddenly became aware of her watching them and sprang apart. The patient remembered seeing her mother hastily pulling up the bedclothes around her to cover her nakedness. Her father, meanwhile, rolled over half on his back, half on his left side. The patient noticed his erection and then saw him lift up his left leg as he sat up and yelled at her angrily to go to sleep. It was not easy for the patient to communicate these memories. She spoke haltingly in a low voice and was visibly ashamed and anxious throughout the whole recital of the dream and its associations. She discharged a great quantity of affect, but after doing so, appeared considerably relaxed, relieved, and composed. On her return to the psychiatric ward, she was observed to be cheerful and outgoing with the ward personnel and other patients. Of particular note was that she no longer experienced any anxiety and had no recurrence of the sexual images involving her father that had previously been so deeply distressing. The patient was discharged a short while later after a further series of psychotherapeutic interviews, and when seen for a follow-up visit 2 months later, she reported continued emotional calm and comfort, without recurrence of psychiatric symptoms. DIAGNOSIS Generalized anxiety disorder is characterized by a pattern of frequent, persistent worry and anxiety that is out of proportion to the impact of the event or circumstance that is the focus of the worry. The distinction between generalized anxiety disorder and normal anxiety is emphasized by the use of the word “excessive” in the criteria and by the specification that the symptoms cause significant impairment or distress. DSM-5 diagnostic criteria for generalized anxiety disorder are listed in Table 9.6-2. Table 9.6-2 DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

CLINICAL FEATURES The essential characteristics of generalized anxiety disorder are sustained and excessive anxiety and worry accompanied by either motor tension or restlessness. The anxiety is excessive and interferes with other aspects of a person’s life. This pattern must occur more days than not for at least 3 months. The motor tension is most commonly manifested as shakiness, restlessness, and headaches. Patients with generalized anxiety disorder usually seek out a general practitioner or internist for help with a somatic symptom. Alternatively, the patients go to a specialist for a specific symptom (e.g., chronic diarrhea). A specific nonpsychiatric medical disorder is rarely found, and patients vary in their doctor-seeking behavior. Some patients accept a diagnosis of generalized anxiety disorder and the appropriate

treatment; others seek additional medical consultations for their problems. Mr. G was a successful, married, 28-year-old teacher who presented for a psychiatric evaluation to treat mounting symptoms of worry and anxiety. Mr. G noted that for the preceding year, he had become more and more worried about his job performance. For example, although he had always been a respected and popular lecturer, he found himself worrying more and more about his ability to engage students and convey material effectively. Similarly, although he had always been financially secure, he increasingly worried that he was going to lose his wealth due to unexpected expenses. Mr. G noted frequent somatic symptoms that accompanied his worries. For example, he often felt tense and irritable while he worked and spent time with his family, and he had difficulty distracting himself from worries about the upcoming challenges for the next day. He reported feeling increasingly restless, especially at night, when his worries kept him from falling asleep. (Courtesy of Erin B. McClure-Tone, Ph.D., and Daniel S. Pine, M.D.) DIFFERENTIAL DIAGNOSIS As with other anxiety disorders, generalized anxiety disorder must be differentiated from both medical and psychiatric disorders. Neurological, endocrinological, metabolic, and medication-related disorders similar to those considered in the differential diagnosis of panic disorder must be considered in the differential diagnosis of generalized anxiety disorder. Common co-occurring anxiety disorders also must be considered, including panic disorder, phobias, OCD, and PTSD. To meet criteria for generalized anxiety disorder, patients must both exhibit the full syndrome, and their symptoms also cannot be explained by the presence of a comorbid anxiety disorder. To diagnose generalized anxiety disorder in the context of other anxiety disorders, it is most important to document anxiety or worry related to circumstances or topics that are either unrelated, or only minimally related, to other disorders. Proper diagnosis involves both definitively establishing the presence of generalized anxiety disorder and properly diagnosing other anxiety disorders. Patients with generalized anxiety disorder frequently develop major depressive disorder. As a result, this condition must also be recognized and distinguished. The key to making a correct diagnosis is documenting anxiety or worry that is unrelated to the depressive disorder. COURSE AND PROGNOSIS The age of onset is difficult to specify; most patients with the disorder report that they have been anxious for as long as they can remember. Patients usually come to a clinician’s attention in their 20s, although the first contact with a clinician can occur at virtually any age. Only one-third of patients who have generalized anxiety disorder seek psychiatric treatment. Many go to general practitioners, internists, cardiologists,

pulmonary specialists, or gastroenterologists, seeking treatment for the somatic component of the disorder. Because of the high incidence of comorbid mental disorders in patients with generalized anxiety disorder, the clinical course and prognosis of the disorder are difficult to predict. Nonetheless, some data indicate that life events are associated with the onset of generalized anxiety disorder: The occurrence of several negative life events greatly increases the likelihood that the disorder will develop. By definition, generalized anxiety disorder is a chronic condition that may well be lifelong. TREATMENT The most effective treatment of generalized anxiety disorder is probably one that combines psychotherapeutic, pharmacotherapeutic, and supportive approaches. The treatment may take a significant amount of time for the involved clinician, whether the clinician is a psychiatrist, a family practitioner, or another specialist. Psychotherapy The major psychotherapeutic approaches to generalized anxiety disorder are cognitivebehavioral, supportive, and insight oriented. Data are still limited on the relative merits of those approaches, although the most sophisticated studies have examined cognitivebehavioral techniques, which seem to have both short-term and long-term efficacy. Cognitive approaches address patients’ hypothesized

cognitive distortions directly, and behavioral approaches address somatic symptoms directly. The major techniques used in behavioral approaches are relaxation and biofeedback. Some preliminary data indicate that the combination of cognitive and behavioral approaches is more effective than either technique used alone. Supportive therapy offers patients reassurance and comfort, although its long-term efficacy is doubtful. Insight-oriented psychotherapy focuses on uncovering unconscious conflicts and identifying ego strengths. The efficacy of insightoriented psychotherapy for generalized anxiety disorder is found in many anecdotal case reports, but large controlled studies are lacking. Most patients experience a marked lessening of anxiety when given the opportunity to discuss their difficulties with a concerned and sympathetic physician. If clinicians discover external situations that are anxiety provoking, they may be able—alone or with the help of the patients or their families—to change the environment and thus reduce the stressful pressures. A reduction in symptoms often allows patients to function effectively in their daily work and relationships and thus gain new rewards and gratification that are themselves therapeutic. In the psychoanalytic perspective, anxiety sometimes signals unconscious turmoil that deserves investigation. The anxiety can be normal, adaptive, maladaptive, too intense, or too mild, depending on the circumstances. Anxiety appears in numerous situations over the course of the life cycle; in many cases, symptom relief is not the most appropriate course of action. For patients who are psychologically minded and motivated to understand the sources of their anxiety, psychotherapy may be the treatment of choice. Psychodynamic therapy

proceeds with the assumption that anxiety can increase with effective treatment. The goal of the dynamic approach may be to increase the patient’s anxiety tolerance (a capacity to experience anxiety without having to discharge it), rather than to eliminate anxiety. Empirical research indicates that many patients who have successful psychotherapeutic treatment may continue to experience anxiety after termination of the psychotherapy, but their increased ego mastery allows them to use the anxiety symptoms as a signal to reflect on internal struggles and to expand their insight and understanding. A psychodynamic approach to patients with generalized anxiety disorder involves a search for the patient’s underlying fears. B, a 28-year-old man with a history of a generalized anxiety disorder, was a former adolescent alcohol abuser now involved in Alcoholics Anonymous (AA). Because of sexual side effects, he was unwilling to take SSRI antidepressants, buspirone (BuSpar) had been ineffective, and gabapentin (Neurontin) was too sedating. Clonazepam (Klonopin) was effective, but B’s continued participation in AA led to pressures from AA peers to give up benzodiazepines. Partly because of these pressures, B sought psychodynamic therapy with a psychiatrist. When the psychiatrist suggested that he begin tapering clonazepam, B balked, worried that he would become more anxious. The therapist suggested that it might be useful to bring his anxiety to sessions if their task really was going to be to learn more about his anxiety. On a tapering dose of clonazepam B’s anxiety increased. He complained that his male therapist was unempathic, making B suffer with anxiety while the therapist watched and did nothing. As the treatment unfolded, the therapist learned B had been especially close to his mother, who, with B, had been the target of criticism from his often absent, short-tempered, mean-spirited alcoholic father. B’s mother had surgery and chemotherapy for breast cancer when B was 10 years old. It was shortly after this that B’s anxiety symptoms began. When clonazepam was discontinued, there was an outburst of anger at the therapist for making B suffer so much. The therapist quietly accepted B’s anger at him, noting that he had asked B to endure more anxiety, while leaving him alone and on his own most of the week. When he suggested that B had found in the therapist his absent and sadistic father, B thought this made sense, and he began to trust the

therapist more. B said he realized that the therapist could endure and understand his anger without needing to retaliate and that he was sticking to a treatment plan they had agreed to from the outset. As the alliance deepened, B struggled to put words to his experience of anxiety. B spoke more of his attachment to his mother and to the way he would cling to her to support her, pressing himself against her ample bosom, while his father would rage at them both while drunk, sometimes suggesting that B's clinging to her was unnatural and inspired by lust. B reported a dream in one session in which he watched passively, frozen with fear and guilt and unable to move, as a man murdered and dismembered a naked woman. B's associations to the dream led to painful memories of his mother's disfiguring

surgery and to his guilt about not having been able to stop his father from angrily criticizing her both before and after the surgery. B then added there was another part of the dream he had left out because of shame. He had been sexually aroused during the dream. B suddenly reported an intrusive thought that upset him—a thought that the breast cancer had come because he had been unable to protect his mother—and because he had been aroused by her breasts. B wept for the first time in the therapy. Over time the therapist and patient explored the dream and his intrusive thoughts, learning that B felt guilty about having caused his mother's illness and disfiguring surgery not only because he could not protect her from father's rages but also because he felt guilty and ashamed about his attraction to his mother's breasts. He spoke of the way his father's drunken accusation of lust toward his mother was right. He feared, too, that he would be disfigured because of a disease or accident, perhaps by castration, for what he had done to his mother. It was not easy for B to explore these feelings, but as he did, his anxiety diminished. (Courtesy of Eric M. Plakun, M.D.) Pharmacotherapy The decision to prescribe an anxiolytic to patients with generalized anxiety disorder should rarely be made on the first visit. Because of the long-term nature of the disorder, a treatment plan must be carefully thought out. The three major drugs to be considered for the treatment of generalized anxiety disorder are benzodiazepines, the SSRIs, buspirone (BuSpar), and venlafaxine (Effexor). Other drugs that may be useful are the tricyclic drugs (e.g., imipramine [Tofranil]), antihistamines, and the β-adrenergic antagonists (e.g., propranolol [Inderal]) (Table 9.6-3). Table 9.6-3 Common Medications for the Treatment of Recurrent Anxiety

Although drug treatment of generalized anxiety disorder is sometimes seen as a 6- to 12-month treatment, some evidence indicates that treatment should be long term, perhaps lifelong. About 25 percent of patients relapse in the first month after the discontinuation of therapy, and 60 to 80 percent relapse over the course of the next year. Although some patients become dependent on the benzodiazepines, tolerance rarely develops to the therapeutic effects of the benzodiazepines, buspirone, venlafaxine, or the SSRIs. Benzodiazepines. Benzodiazepines have been the drugs of choice for generalized anxiety disorder. They can be prescribed on an as-needed basis, so that patients take a rapidly acting benzodiazepine when they feel particularly anxious. The alternative approach is to prescribe benzodiazepines for a limited period, during which psychosocial therapeutic approaches are implemented. Several problems are associated with the use of benzodiazepines in generalized anxiety disorder. About 25 to 30 percent of all patients fail to respond, and tolerance

and dependence can occur. Some patients also experience impaired alertness while taking the drugs and therefore are at risk for accidents involving automobiles and machinery. The clinical decision to initiate treatment with a benzodiazepine should be considered and specific. The

patient’s diagnosis, the specific target symptoms, and the duration of treatment should all be defined, and the information should be shared with the patient. Treatment for most anxiety conditions lasts for 2 to 6 weeks followed by 1 or 2 weeks of tapering drug use before it is discontinued. The most common clinical mistake with benzodiazepine treatment is to continue treatment indefinitely. For the treatment of anxiety, it is usual to begin giving a drug at the low end of its therapeutic range and to increase the dosage to achieve a therapeutic response. The use of a benzodiazepine with an intermediate half-life (8 to 15 hours) will likely avoid some of the adverse effects associated with the use of benzodiazepines with long half-lives, and the use of divided doses prevents the development of adverse effects associated with high peak plasma levels. The improvement produced by benzodiazepines may go beyond a simple antianxiety effect. For example, the drugs may cause patients to regard various occurrences in a positive light. The drugs can also have a mild disinhibiting action, similar to that observed after ingesting modest amounts of alcohol. Buspirone. Buspirone is a 5-HT1A receptor partial agonist and is most likely effective in 60 to 80 percent of patients with generalized anxiety disorder. Data indicate that buspirone is more effective in reducing the cognitive symptoms of generalized anxiety disorder than in reducing the somatic symptoms. Evidence also indicates that patients who have previously had treatment with benzodiazepines are not likely to respond to treatment with buspirone. The lack of response may be caused by the absence, with buspirone treatment, of some of the nonanxiolytic effects of benzodiazepines (e.g., muscle relaxation and the additional sense of well-being). The major disadvantage of buspirone is that its effects take 2 to 3 weeks to become evident, in contrast to the almost immediate anxiolytic effects of the benzodiazepines. One approach is to initiate benzodiazepine and buspirone use simultaneously and then taper off the benzodiazepine use after 2 to 3 weeks, at which point the buspirone should have reached its maximal effects. Some studies have also reported that long-term combined treatment with benzodiazepine and buspirone may be more effective than either drug alone. Buspirone is not an effective treatment for benzodiazepine withdrawal. Venlafaxine. Venlafaxine is effective in treating the insomnia, poor concentration, restlessness, irritability, and excessive muscle tension associated with generalized anxiety disorder. Venlafaxine is a nonselective inhibitor of the reuptake of three biogenic amines—serotonin; norepinephrine; and, to a lesser extent, dopamine. Selective Serotonin Reuptake Inhibitors. SSRIs may be effective, especially for patients with comorbid depression. The prominent disadvantage of SSRIs, especially

fluoxetine (Prozac), is that they can transiently increase anxiety and cause agitated states. For this reason, the SSRIs sertraline (Zoloft), citalopram (Celexa), or paroxetine (Paxil) are better choices in patients with high anxiety disorder. It is reasonable to begin treatment with sertraline, citalopram, or paroxetine plus a benzodiazepine and then to taper benzodiazepine use after 2 to 3 weeks. Further studies are needed to determine whether SSRIs are as effective for generalized anxiety disorder as they are for panic disorder and OCD. Other Drugs. If conventional pharmacological treatment (e.g., with buspirone or a benzodiazepine) is ineffective or not completely effective, then a clinical reassessment is indicated to rule out comorbid conditions, such as depression, or to better understand the patient’s environmental stresses. Other drugs that have proved useful for generalized anxiety disorder include the tricyclic and tetracyclic drugs. The β-adrenergic receptor antagonists may reduce the somatic manifestations of anxiety but not the underlying condition, and their use is usually limited to situational anxieties, such as performance anxiety. REFERENCES Cuijpers, P., Sijbrandij, M., Koole, S., Huibers, M., Berking, M., & Andersson, G. Psychological treatment of generalized anxiety disorder: A meta-analysis. Clin Psychol Rev. 2014. Etkin A, Prater

KE, Hoeft F, Menon V, Schatzberg AF. Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. Am J Psychiatry. 2010;167:545. Goodwin RD, Stein DJ. Anxiety disorders and drug dependence: Evidence on sequence and specificity among adults. Psych Clin Neurosci. 2013;67:167. Hill N, Joubert L, Epstein I. Encouraging self-management in chronically ill patients with comorbid symptoms of depression and anxiety: An emergency department study and response. Soc Work Health Care. 2013;52:207. Lenze EJ, Mantella RC, Shi P, Goate AM, Nowotny P, Butters MA, Andreescu C, Thompson PA, Rollman BL. Elevated cortisol in older adults with generalized anxiety disorder is reduced by treatment: A placebo-controlled evaluation of escitalopram. Am J Geriatric Psychiatry. 2011;19:482. Lorenz RA, Jackson CW, Saltz M. Adjunctive use of atypical antipsychotics for treatment-resistant generalized anxiety disorder. Pharmacotherapy. 2010;30:942. Maslowsky J, Mogg K, Bradley BP, McClure-Tone E, Ernst M, Pine DS, Monk CS. A preliminary investigation of neural correlates of treatment in adolescents with generalized anxiety disorder. J Child Adolescent Psychcopharm. 2010;20:105. McClure-Tone EB, Pine DS. Clinical features of the anxiety disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1844. Newman MG, Castonguay LG, Borkovec TD, Fisher AJ, Boswell JF, Szkodny LE, Nordberg SS. A randomized controlled trial of cognitive-behavioral therapy for generalized anxiety disorder with integrated techniques from emotion-focused and interpersonal therapies. J Consult Clin Psychol. 2011;79:171. Newman MG, Przeworski A, Fisher AJ, Borkovec TD. Diagnostic comorbidity in adults with generalized anxiety disorder: Impact of comorbidity on psychotherapy outcome and impact of psychotherapy on comorbid diagnoses. Behav Ther. 2010;41:59. Ouimet AJ, Covin R, Dozois DJA. Generalized anxiety disorder. In: Sturmey P, Hersen M, eds. Handbook of Evidence-Based

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Practice in Clinical Psychology. Vol 2: Adult Disorders. Hoboken: John Wiley & Sons; 2012:651. Ritter MR, Blackmore MA, Heimberg RG. Generalized anxiety disorder. In: McKay D, Abramowitz JS, Taylor S, eds. Cognitive Behavioral Therapy for Refractory Cases: Turing Failure Into Success. Washington, DC: American Psychological Association; 2010. Uebelacker L, Weisberg R, Millman M, Yen S, Keller M. Prospective study on risk factors for suicidal behavior in individuals with anxiety disorders. Psychol Med. 2013;43:1465. 9.7 Other Anxiety Disorders ANXIETY DISORDER ATTRIBUTABLE TO ANOTHER MEDICAL CONDITION Many medical disorders are associated with anxiety. Symptoms can include panic attacks, generalized anxiety, and other signs of distress. In all cases, the signs and symptoms will be due to the direct physiological effects of the medical condition. Epidemiology The occurrence of anxiety symptoms related to general medical conditions is common, although the incidence of the disorder varies for each specific general medical condition. Etiology A wide range of medical conditions can cause symptoms similar to those of anxiety disorders (Table 9.7-1). Hyperthyroidism, hypothyroidism, hypoparathyroidism, and vitamin B12 deficiency are frequently associated with anxiety symptoms. A pheochromocytoma produces epinephrine, which can cause paroxysmal episodes of anxiety symptoms. Other medical conditions, such as cardiac arrhythmia, can produce physiological symptoms of panic disorder. Hypoglycemia can also mimic the symptoms of an anxiety disorder. The diverse medical conditions that can cause symptoms of anxiety disorder may do so through a common mechanism that involves both the noradrenergic system and the serotonergic system. Each of these conditions is characterized by prominent anxiety that arises as the direct result of some underlying physiological perturbation. Table 9.7-1 Disorders Associated with Anxiety

Diagnosis The diagnosis of anxiety disorder attributable to another medical condition requires the presence of symptoms of an anxiety disorder caused by one or more medical illnesses. The DSM-5 suggests that clinicians to specify whether the disorder is characterized by symptoms of generalized anxiety or panic attacks. Clinicians should have an increased level of suspicion for the diagnosis when chronic or paroxysmal anxiety is associated with a physical disease known to cause such symptoms in some patients. Paroxysmal bouts of hypertension in an anxious patient may indicate that a workup for a pheochromocytoma is appropriate. A general medical workup may reveal diabetes, an adrenal tumor, thyroid disease, or a neurological condition. For example, some patients with complex partial epilepsy have extreme

episodes of anxiety or fear as their only manifestation of the epileptic activity. Clinical Features The symptoms of anxiety disorder due to a general medical condition can be identical to those of the primary anxiety disorders. A syndrome similar to panic disorder is the most common clinical picture, and a syndrome similar to a phobia is the least common. Panic Attacks. Patients who have cardiomyopathy may have the highest incidence of panic disorder secondary to a general medical condition. One study reported that 83 percent of patients with cardiomyopathy awaiting cardiac transplantation had panic disorder symptoms. Increased noradrenergic tone in these patients may be the provoking stimulus for the panic attacks. In some studies, about 25 percent of patients with Parkinson's disease and chronic obstructive pulmonary disease have symptoms of panic disorder. Other medical disorders associated with panic disorder include chronic pain, primary biliary cirrhosis, and epilepsy, particularly when the focus is in the right parahippocampal gyrus. Generalized Anxiety. A high prevalence of generalized anxiety disorder symptoms has been reported in patients with Sjögren's syndrome, and this rate may be related to the effects of Sjögren's syndrome on cortical and subcortical functions and thyroid function. The highest prevalence of generalized anxiety disorder symptoms in a medical disorder seems to be in Graves' disease (hyperthyroidism), in which as many as two-thirds of all patients meet the criteria for generalized anxiety disorder. A 86-year-old retired chemical engineer sought help for the onset of a series of attacks over the preceding 4 months in which he experienced marked apprehension, restlessness, a sense that the "walls were caving in," and the need to "get air" to relieve his sense of discomfort. These events typically occurred during the night and awakened him from sound sleep. To feel better, he would need to stick his head out of an open window, regardless of how cold it was outside. His symptoms would gradually improve over 15 to 20 minutes, but complete resolution of these symptoms took a full day. In response to pointed questioning, the patient reported sweating, dizziness, and shortness of breath during these episodes. He imagined that he would die if he could not open the window. He denied palpitations, choking sensations, paresthesia, and nausea. The patient recalled a similar series of attacks almost 30 years earlier during a period of time in which he frequently needed to travel and hence was away from home because of work obligations. The patient denied depressed mood, anhedonia, recent sleep dysfunctions, change in appetite or weight, decreased energy, and feelings of worthlessness. His medical history was notable for a right basal ganglia stroke 6 months earlier. He had a history of hypertension, borderline diabetes, and benign prostatic hypertrophy. Laboratory study results were unremarkable.

A diagnosis of anxiety disorder due to stroke, with panic attacks, was made. The patient was prescribed alprazolam (Xanax), 0.5 mg orally twice a day as needed for panic attacks, and started on escitalopram (Lexapro), 10 mg per day. At a follow-up visit, the patient reported complete resolution of his anxiety symptoms. He remained taking the escitalopram but no longer required the alprazolam. (Courtesy of LL Lavery, M.D., and EM Whyte, M.D.) Phobias. Symptoms of phobias appear to be uncommon, although one study reported a 17 percent prevalence of symptoms of social phobia in patients with Parkinson's disease. Older persons with balance difficulties often complain of a fear of falling, which may express itself by their being unwilling or fearful of walking. Laboratory Examination A targeted work-up is required when an anxiety disorder due to another medical condition is being considered as part of the differential diagnosis. If possible, tests should be selected to rule in specific diagnoses suggested by the patient's somatic symptoms (if present). Test to consider include complete book count, electrolytes, glucose, blood urea nitrogen, creatinine, liver function tests, calcium, magnesium, phosphorus, thyroid function tests, and urine

toxicology. Occasionally, additional studies may be indicated to rule out a pheochromocytoma (e.g., urinary catecholamines), a seizure disorder (e.g., EEG), cardiac arrhythmia (e.g., Holter monitoring), and pulmonary disease (pulse oximetry, arterial blood gases). Brain imaging may be useful in ruling out demyelinating disorder, tumor, stroke, or hydrocephalus and is especially important if the anxious individual reports neurological symptoms (e.g., headache, motor or sensory changes, and dizziness), although such complaints may represent somatic manifestations of primary anxiety disorders. Lumbar puncture may be appropriate if an inflammatory or infectious cause is suspected. Differential Diagnosis Anxiety, as a symptom, can be associated with many psychiatric disorders in addition to the anxiety disorders themselves. A mental status examination is necessary to determine the presence of mood symptoms or psychotic symptoms that may suggest another psychiatric diagnosis. For a clinician to conclude that a patient has an anxiety disorder caused by a general medical condition, the patient should clearly have anxiety as the predominant symptom and should have a specific causative nonpsychiatric medical disorder. To ascertain the degree to which a general medical condition is causative for the anxiety, the clinician should evaluate the timeline between the medical condition and the anxiety symptoms, the age of onset (primary anxiety disorders usually have their onset before age 35 years), and the patient's family history of both anxiety disorders and relevant general medical conditions (e.g., hyperthyroidism). A diagnosis

of adjustment disorder with anxiety must also be considered in the differential diagnosis. Course and Prognosis The unremitting experience of anxiety can be disabling and can interfere with every aspect of life, including social, occupational, and psychological functioning. A sudden increase in anxiety level may prompt an affected person to seek medical or psychiatric help more quickly than when the onset is insidious. The treatment or the removal of the primary medical cause of the anxiety usually initiates a clear course of improvement in the anxiety disorder symptoms. In some cases, however, the anxiety disorder symptoms continue even after the primary medical condition is treated (e.g., after an episode of encephalitis). Some symptoms linger for a longer time than other anxiety disorder symptoms. When anxiety disorder symptoms are present for a significant period after the medical disorder has been treated, the remaining symptoms should probably be treated as if they were primary—that is, with psychotherapy, pharmacotherapy, or both. Treatment The primary treatment for anxiety disorder due to a general medical condition is to treat the underlying medical condition. If a patient also has an alcohol or other substance use disorder, this disorder must also be addressed therapeutically to gain control of the anxiety disorder symptoms. If the removal of the primary medical condition does not reverse the anxiety disorder symptoms, treatment of these symptoms should follow the treatment guidelines for the specific mental disorder. In general, behavioral modification techniques, anxiolytic agents, and serotonergic antidepressants have been the most effective treatment modalities. SUBSTANCE-INDUCED ANXIETY DISORDER Substance-induced disorder is the direct result of a toxic substance, including drugs of abuse, medication, poison, and alcohol, among others. Epidemiology Substance-induced anxiety disorder is common, both as the result of the ingestion of socalled recreational drugs and as the result of prescription drug use. Etiology A wide range of substances can cause symptoms of anxiety that can mimic any of the DSM-5 anxiety disorders. Although sympathomimetics, such as amphetamine, cocaine, and caffeine, have been most associated with the production of anxiety disorder symptoms, many serotonergic drugs (e.g., LSD and MDMA) can also cause both acute and chronic anxiety syndromes in users. A wide range of prescription medications is also associated with the production of anxiety disorder symptoms in susceptible persons.

Diagnosis The diagnostic criteria for substance-induced anxiety disorder require the presence of prominent anxiety or panic attacks. The DSM-5 guidelines state that the symptoms should have developed during the use of the substance or within 1 month of the cessation of substance use; however, clinicians may have difficulty determining the relation between substance exposure and anxiety symptoms. The structure of the diagnosis includes specification of (1) the substance (e.g., cocaine), (2) the appropriate state during the onset (e.g., intoxication), and (3) the specific symptom pattern (e.g., panic attacks). Clinical Features The associated clinical features of substance-induced anxiety disorder vary with the particular substance involved. Even infrequent use of psychostimulants can result in anxiety disorder symptoms in some persons. Cognitive impairments in comprehension, calculation, and memory can be associated with anxiety disorder symptoms. These cognitive deficits are usually reversible when the substance use is stopped. Virtually everyone who drinks alcohol, on at least a few occasions, has used it to reduce anxiety, most often social anxiety. In contrast, carefully controlled studies have found that the effects of alcohol on anxiety are variable and can be significantly affected by gender, the amount of alcohol ingested, and cultural attitudes. Nevertheless, alcohol use disorders and other substance-related disorders are commonly associated with anxiety disorders. Alcohol use disorders are about four times more common among patients with panic disorder than among the general population and about two and a half times more common among patients with phobias. Several studies have reported data indicating that genetic diatheses for both anxiety disorders and alcohol use disorders can exist in some families. Differential Diagnosis The differential diagnosis for substance-induced anxiety disorder includes the primary anxiety disorders; anxiety disorder due to a general medical condition (for which the patient may be receiving an implicated drug); and mood disorders, which are frequently accompanied by symptoms of anxiety disorders. Personality disorders and malingering must be considered in the differential diagnosis, particularly in some urban emergency departments. Course and Prognosis The course and prognosis generally depend on removal of the causally involved substance and the long-term ability of the affected person to limit use of the substance. The anxiogenic effects of most drugs are reversible. When the anxiety does not reverse with cessation of the drug, clinicians should reconsider the diagnosis of substance-

induced anxiety disorder or consider the possibility that the substance caused irreversible brain damage. Treatment The primary treatment for substance-induced anxiety disorder is the removal of the causally involved substance. Treatment then must focus on finding an alternative treatment if the substance was a medically indicated drug, on limiting the patient’s exposure if the substance was introduced through environmental exposure, or on treating the underlying substance-related disorder. If anxiety disorder symptoms continue even after stopping substance use, treatment of the anxiety disorder symptoms with appropriate psychotherapeutic or pharmacotherapeutic modalities may be appropriate. MIXED ANXIETY-DEPRESSIVE DISORDER Mixed anxiety-depressive disorder describes patients with both anxiety and depressive symptoms who do not meet the diagnostic criteria for either an anxiety disorder or a mood disorder. The combination of depressive and anxiety symptoms results in significant functional impairment for the affected person. The condition may be particularly prevalent in primary care practices and outpatient mental health clinics. Opponents have argued that the availability of the diagnosis may discourage clinicians from taking the necessary time to obtain a complete psychiatric history to differentiate true depressive disorders from true anxiety disorders. In Europe and especially in China, many of these patients are given a diagnosis of neurasthenia. Epidemiology The coexistence of major depressive disorder and panic disorder is common. As many as two-thirds of all patients with depressive symptoms have

prominent anxiety symptoms, and one-third may meet the diagnostic criteria for panic disorder. Researchers have reported that 20 to 90 percent of all patients with panic disorder have episodes of major depressive disorder. These data suggest that the coexistence of depressive and anxiety symptoms, neither of which meets the diagnostic criteria for other depressive or anxiety disorders, may be common. Presently, however, formal epidemiological data on mixed anxiety-depressive disorder are not available. Nevertheless, some clinicians and researchers have estimated that the prevalence of the disorder in the general population is as high as 10 percent and as high as 50 percent in primary care clinics, although conservative estimates suggest a prevalence of about 1 percent in the general population. Etiology Four principal lines of evidence suggest that anxiety symptoms and depressive symptoms are causally linked in some affected patients. First, several investigators have

reported similar neuroendocrine findings in depressive disorders and anxiety disorders, particularly panic disorder, including blunted cortisol response to adrenocorticotropic hormone, blunted growth hormone response to clonidine (Catapres), and blunted thyroid-stimulating hormone and prolactin responses to thyrotropin-releasing hormone. Second, several investigators have reported data indicating that hyperactivity of the noradrenergic system is causally relevant to some patients with depressive disorders and with panic disorder. Specifically, these studies have found elevated concentrations of the norepinephrine metabolite (MHPG) in the urine, the plasma, or the CSF of depressed patients and patients with panic disorder who were actively experiencing a panic attack. As with other anxiety and depressive disorders, serotonin and GABA may also be causally involved in mixed anxiety-depressive disorder. Third, many studies have found that serotonergic drugs, such as fluoxetine (Prozac) and clomipramine (Anafranil), are useful in treating both depressive and anxiety disorders. Fourth, a number of family studies have reported data indicating that anxiety and depressive symptoms are genetically linked in at least some families. Diagnosis The diagnostic criteria for mixed anxiety-depressive disorder require the presence of subsyndromal symptoms of both anxiety and depression and the presence of some autonomic symptoms, such as tremor, palpitations, dry mouth, and the sensation of a churning stomach. Some preliminary studies have indicated that the sensitivity of general practitioners to a syndrome of mixed anxiety-depressive disorder is low, although this lack of recognition may reflect the lack of an appropriate diagnostic label for the patients. Clinical Features The clinical features of mixed anxiety-depressive disorder combine symptoms of anxiety disorders and some symptoms of depressive disorders. In addition, symptoms of autonomic nervous system hyperactivity, such as gastrointestinal complaints, are common and contribute to the high frequency with which the patients are seen in outpatient medical clinics. Differential Diagnosis The differential diagnosis includes other anxiety and depressive disorders and personality disorders. Among the anxiety disorders, generalized anxiety disorder is most likely to overlap with mixed anxiety-depressive disorder. Among the mood disorders, dysthymic disorder and minor depressive disorder are most likely to overlap with mixed anxiety-depressive disorder. Among the personality disorders, avoidant, dependent, and obsessive-compulsive personality disorders may have symptoms that resemble those of mixed anxiety-depressive disorder. A diagnosis of a somatoform disorder should also be considered. Only a psychiatric history, a mental status examination, and a working

knowledge of the specific criteria can help clinicians differentiate among these conditions. The prodromal signs of schizophrenia may show itself as a mixed picture of mounting anxiety and depression with eventual onset of psychotic symptoms. Course and Prognosis On the basis of

clinical data to date, patients seem to be equally likely to have prominent anxiety symptoms, prominent depressive symptoms, or an equal mixture of the two symptoms at onset. During the course of the illness, anxiety or depressive symptoms may alternate in their predominance. The prognosis is not known. Treatment Because adequate studies comparing treatment modalities for mixed anxiety-depressive disorder are not available, clinicians are probably most likely to provide treatment based on the symptoms present, their severity, and the clinician's own level of experience with various treatment modalities. Psychotherapeutic approaches may involve time-limited approaches, such as cognitive therapy or behavior modification, although some clinicians use a less structured psychotherapeutic approach, such as insight-oriented psychotherapy. Pharmacotherapy for mixed anxiety-depressive disorder can include antianxiety drugs, antidepressant drugs, or both. Among the anxiolytic drugs, some data indicate that the use of triazolobenzodiazepines (e.g., alprazolam [Xanax]) may be indicated because of their effectiveness in treating depression associated with anxiety. A drug that affects the serotonin 5-HT1A receptor, such as buspirone (BuSpar), may also be indicated. Among the antidepressants, despite the noradrenergic theories linking anxiety disorders and depressive disorders, the serotonergic antidepressants may be most effective in treating mixed anxiety-depressive disorder. Venlafaxine (Effexor) is an effective antidepressant that has been approved by the FDA for the treatment of depression as well as generalized anxiety disorder and is a drug of choice in the combined disorder. REFERENCES Algeria AA, Hasin DS, Nunes EV, Liu SM, Davies C, Grand BF, Blanco C. Comorbidity of generalized anxiety disorder and substance use disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2010;71:1187. Beard C, Weisberg RB, Keller MB. Health-related quality of life across the anxiety disorders: Findings from a sample of primary care patients. J Anxiety Disord. 2010;24:559. Campbell-Sills L, Stein MB, Sherbourne CD, Craske MG, Sullivan G, Golinelli D, Lang AJ, Chavira DA, Bystritsky A, Rose RD, Welch SS, Kallenberg GA, Roy-Byrne P. Effects of medical comorbidity on anxiety treatment outcomes in primary care. Psychosom Med. 2013; 75:713. Comer JS, Blanco C, Hasin DS, Liu SM, Grant BF, Turner JB, Olfson M. Health-related quality of life across the anxiety disorders. J Clin Psych. 2011;72:43. Galbraith, T., Heimberg, RG, Wang, S., Schneier, FR, & Blanco, C. Comorbidity of social anxiety disorder and antisocial

personality disorder in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). J Anxiety Disord. 2014;28(1):57–66. Goodwin RD, Stein DJ. Anxiety disorders and drug dependence: Evidence on sequence and specificity among adults. Psych Clin Neurosci. 2013;67:167. Hill N, Joubert L, Epstein I. Encouraging self-management in chronically ill patients with comorbid symptoms of depression and anxiety: An emergency department study and response. Soc Work Health Care. 2013;52:207. Kroenke K, Outcalt S, Krebs E, Bair MJ, Wu J, Chumbler N, Yu Z. Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. Gen Hosp Psych. 2013; 35:359. McClure-Tone EB, Pine DS. Clinical features of anxiety disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1844. Pao M, Bosk A. Anxiety in medically ill children/adolescents. Depress Anxiety. 2011;28:40. Pontone GM, Williams JR, Anderson K, Chase G, Goldstein S, Grill S, Hirsch ES, Lehmann S, Little JT, Margolis RL, Rabins PV, Weiss H, Marsh L. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Mov Disord. 2009;24:1333. Roy-Byrne P, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang AJ, Bystritsky A, Welch SS, Chavira DA, Golinelli D, Campbell-Sills L, Sherbourne CD, Stein MB. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: A randomized controlled trial. JAMA. 2010;303:1921.