06 - 9.6 Generalized Anxiety Disorder

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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

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