Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a common disorder, with a prevalence in the range of 1% to 6% in the United States. The disorder is characterized by chronic, uncontrollable worry compounded by physiologic symptoms such as restlessness, muscle tension, impaired concentration, and disturbed sleep. Significant impairment in social and occupational functioning can occur with GAD, and it has been estimated that 6 days a month are lost to missed or shortened work days for individuals with the disorder. Progress in both research and clinical recognition of GAD has been hampered by the shifting and diffuse nature of the disorder's symptoms, changes in the diagnostic criteria for GAD over time, and the high rate of psychiatric and medical comorbidity. Recently, brief screening questions have been developed to aid in diagnosing the disorder. There has also been a resurgence of interest in research on both the underlying biology and the treatment of GAD. This article provides a review of our current knowledge about the epidemiology, biology, comorbidity, associated impairment, and treatment of GAD, including pharmacotherapy and psychosocial therapies.

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Definition

Generalized anxiety disorder was first defined in 1980, in DSM-III, as a disorder of uncontrollable and diffuse anxiety or worry that is excessive or unrealistic and lasts 1 month or longer (1). Previously, these symptoms had been considered part of "anxiety neurosis," in which chronic worry and panic attacks lumped together (2). Freud's original definition of anxiety neurosis included chronic apprehension or anxious expectation, general irritability, anxiety attacks, and secondary phobic avoidance (3). In DSM-III, the distinctive paroxysmal experience of panic attacks was conceptualized as a separate disorder, namely, panic disorder, and the remaining nonspecific anxiety and worry-related symptoms formed the basis of the diagnosis of GAD. This new diagnosis required that the psychophysiologic symptoms listed under the headings "motor tension" and "autonomic hyperactivity" be present chronically; examples include "trembling, fidgeting, easy startle" and "clammy hands, hot or cold spells, and lump in the throat" (1). The DSM-III criteria also specified that symptoms could not be secondary to another general medical or psychiatric disorder.

Since the introduction of this diagnosis, debate has persisted about whether the symptoms of GAD are a prodrome of, residual from, or part of another primary disorder. The uncertainty stems from a number of factors, including the nonspecific focus of anxiety, which may shift over time, and the overlapping symptoms and high prevalence of comorbidity with mood and other anxiety disorders, particularly major depression. Indeed, a bias against GAD as a separate disorder was evident in the first wave of the Epidemiologic Catchment Area survey (4), which did not include GAD as a possible diagnosis in the research diagnostic interview.

In the DSM-III-R criteria (5), partly in response to concerns about whether GAD was a stable, distinct disorder, the duration of symptoms was increased from 1 month to 6 months. Six specific symptoms selected from a list of 18 were also required, including psychophysiologic symptoms such as trembling, dry mouth, nausea, or trouble falling or staying asleep. It was further specified that the focus of the patient's worries be unrelated to another anxiety disorder (i.e., the excessive worry cannot be about having a panic attack, as in panic disorder, or being embarrassed in social or performance situations, as in social phobia). DSM-III-R changed the diagnostic hierarchy rules, however, to allow GAD to be diagnosed in the presence of other disorders, as long as "the focus of persis-tent anxiety and worry is unrelated to any other axis I disorder."

In DSM-IV (6), the criteria were further modified to require that the worries be about "a number of events or activities" and that the person find the worries "difficult to control" (see Table 1). In addition to worry, DSM-IV called for the presence of at least three of six symptoms—restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. GAD symptoms could not occur exclusively during a mood disorder, psychotic disorder, or pervasive developmental disorder, a criterion meant to emphasize the concept of GAD as a separate disorder that persists at least for some time in episodes distinct from those of other disorders.

PREVALENCE

The prevalence of GAD in the general population is 1.2%–6.4%, although the changing diagnostic criteria over the years complicates interpretation of these figures. In the 1980s, the Epidemiologic Catchment Area (ECA) study, using DSM-III criteria in its questionnaire, reported detailed findings such as prevalence rates by gender. However, ECA measurements of GAD have been criticized as somewhat unreliable because only three of the five sites addressed the disorder, and the assessment tools they used for GAD varied (7). In the ECA study, the average current prevalence was 1.3% across the sites, and lifetime prevalence was 5.8%.

The validity of the ECA prevalence rates is supported by similar findings—a current rate of 1.6% and a lifetime rate of 5.1%—in the later National Comorbidity Survey (NCS) (7), which used DSM-III-R criteria for GAD. In the NCS, a diagnosis of GAD was allowed with a concurrent mood or psychotic disorder, an important factor given the previous uncertainty about whether the high rate of psychiatric comorbidity indicates that GAD is not a separate disorder. When cases of GAD that occurred during a mood or psychotic episode were excluded, the lifetime prevalence decreased by only 0.03%,

Table 1. DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder

A.	Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B.	The person finds it difficult to control the worry.
C.	The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). Note: Only one item is required in children. (1) restlessness or feeling keyed up or on edge (2) being easily fatigued (3) difficulty concentrating or mind going blank (4) irritability (5) muscle tension (6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D.	The focus of the anxiety and worry is not confined to features of an axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.
E.	The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
F.	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

showing that comorbidity with other disorders does not account for the presence of GAD. Moreover, only 8% of individuals with GAD reported that their GAD occurred exclusively during a mood or psychotic disorder. Among the individuals with GAD, 9.6% reported that it was their only lifetime psychiatric disorder, and 12.2% reported that the onset of GAD preceded that of any other disorder; these relatively high proportions both suggest that GAD does indeed exist as a separate, diagnosable disorder. In the NCS, predictors of GAD included an age of 24 years or older, being separated, widowed, or divorced, being unemployed, and being a homemaker (7).

Rates of GAD reported in prevalence studies in other countries have been varied but generally similar to those reported in the NCS. In the Netherlands, a past-month rate of 0.8% and a lifetime rate of 2.3% were reported for GAD as defined by DSM-III-R criteria (8). In Australia, 2.8% of interview subjects in the general public met DSM-IV criteria for GAD in the previous 30 days (9).

As with other psychiatric disorders, GAD is found at higher rates in medical settings. This was clearly demonstrated in a 14-country World Health Organization (WHO) study of primary care (10) in which a mean 1-month prevalence of 7.9% was found for GAD on the basis of ICD-10 criteria.

GENDER

GAD occurs more commonly among women, with a lifetime prevalence of nearly 7% for women in community samples, compared with about 4% for men (7). The rate of GAD is particularly elevated among women 44 years of age and older (7, 11). The 14-country WHO study found an average current prevalence of 9.2% among women and 5.7% among men, although gender-specific rates varied substantially among the study sites. In Brazil, for example, the current prevalence of GAD was 26% for women and 14% for men, whereas in China it was 2.1% for women and 1.7% for men, which suggests that cultural and/or genetic factors may contribute to diagnostic prevalence (10).

AGE

Prevalence rates of GAD appear to vary somewhat with age. The diagnosis of GAD has only recently been expanded to include children. Under DSM-III-R criteria, children who had excessive worry, concern about competence, somatic complaints, self-consciousness, excessive need for reassurance, and tension that persisted for at least 6 months were given the diagnosis of overanxious disorder. In DSM-IV, this diagnosis was combined with GAD. Studies of overanxious disorder in children have found prevalence rates ranging from 2.9% to 4.6% among children aged 11 years and under (12, 13), and 3.6% to 7.3% among adolescents (14). In Germany, Wittchen and colleagues, using the diagnostic criteria for GAD with adolescents and young adults aged 14 to 24 years, found lower rates. They reported a lifetime prevalence of 0.8% and a 1-year prevalence of 0.5% (15). It has been hypothesized that GAD has a later onset than other anxiety disorders, perhaps because of an accumulation of chronic stressors over time (16). GAD also may have an onset in late adulthood. Community-based studies of GAD have found prevalence rates of about 4% in individuals aged 65 and over (17).

COMORBIDITY

PSYCHIATRIC COMORBIDITY

As noted, psychiatric comorbidity is common with GAD, which has contributed to the uncertainty about whether GAD is a distinct diagnosis. In the National Comorbidity Survey, major depression was present in 62% of subjects with GAD (7). Dysthymia (40%), alcohol abuse or dependence (38%), social phobia (34%), and simple phobia (35%) were commonly comorbid with GAD. The overall current psychiatric comorbidity rate with GAD was 66.3%, and the lifetime comorbidity was 90.4%. It should be noted, however, that comorbidity rates are high across psychiatric diagnoses in general, at approximately 50% (18).

While some experts on anxiety disorders believe that GAD is clearly a distinct diagnosis, others continue to question whether the symptoms of GAD may instead constitute a prodrome, a residual of a previous disorder, or a severity marker of some other disorder, such as depression or panic disorder. The presence of GAD has been shown to dramatically increase the likelihood of a new major depressive episode occurring within one year of the onset of GAD (odds ratio=62) (19). Support for GAD as a distinct diagnosis from depression was found in a study that analyzed the specific symptoms of GAD and depression on dimensional symptom measures. The study found good discriminant validity, or separateness of symptom groupings, for GAD and depression (20). The occurrence of "pure" GAD, with no other diagnosis, which is found in 10%–18% of persons with the disorder, provides additional support for GAD as a distinct category (7, 21). Differences among patients with GAD have also been found in sociodemographic predictors (22) and

in psychological traits such as suspiciousness, mistrust, and hostility, when compared with patients who have other mood or anxiety disorders (23).

If GAD is distinct from other comorbid psychiatric disorders, one might expect there to be some differences in the genetic and environmental contributions to GAD and the comorbid disorders. Kendler and colleagues studied 1,033 pairs of female twins with major depression and GAD and found that while genetic factors were shared between the two disorders, environmental determinants were distinct (24).

When comorbidity is present, individuals with GAD have greater symptom severity and greater impairment. Comorbidity is associated with a greater degree of interference with daily activities, with more help seeking, medication taking, laboratory tests, hospitalization, conflict with others, and with a poorer outcome for GAD (23). The disability may be due to the GAD, the comorbid disorder, or the combination of the two. Large studies of community samples with GAD and depression suggest that each disorder is independently and approximately equally impairing (25).

MEDICAL COMORBIDITY

GAD may occur more frequently in individuals with certain medical illnesses. There appears to be a higher rate of GAD among individuals with chronic obstructive pulmonary disease than in the general population (26). Similarly, 18 studies of diabetes mellitus in aggregate suggest that 14% of patients with diabetes also have GAD (27). Thyroid disease may also occur at higher rates among patients with GAD than in the general population, as supported by a study of self-reported thyroid disease in patients with GAD (28). In these studies, the order of onset of the disorders is unclear, as is the etiology of the comorbidity. While the pathophysiology of a general medical disease and the stress and functional impairment associated with the disease may each serve as a risk factor for GAD, GAD may also increase the risk of developing some medical disorders. One study reported that, after adjusting for sociodemographic variables as well as psychiatric and medical comorbidity, GAD symptoms had a dose-response relationship, or positive correlation, with the risk of peptic ulcer disease (29).

SCREENING IN THE PRIMARY CARE SETTING

GAD is not well recognized in the primary care setting. For example, in a German survey of over 20,000 patients and their primary care physicians, physicians recognized and diagnosed pure GAD only 34% of the time when it was actually present. In addition, 44% of all patients with pure GAD did not receive treatment or a referral to a specialist. The authors of the study surmised that the vagueness of GAD symptoms and the common somatic presentation tend to confuse primary care providers (30). In an effort to improve the screening, diagnosis, and treatment of GAD, the International Consensus Group on Depression (31) recommends two screening questions for GAD:

1. During the past 4 weeks, have you been bothered by feeling worried, tense, or anxious most of the time?
2. Are you frequently tense, irritable, and having trouble sleeping?

Other screening tools have been developed to improve the detection of common psychiatric disorders by primary care physicians. One approach is a multistep screening process that starts with a 16-item patient-rated checklist. The primary care physician reviews the checklist, which is meant to prompt further questioning about the symptoms related to the checked item. For GAD, a check mark on one of the checklist items of "anxiety" or "nervousness" was found to have a sensitivity of 90% and a specificity of 54% for the disorder (32).

Perhaps the most extensive research screening in medical populations has been done with the Primary Care Evaluation of Mental Disorders (PRIME-MD) instrument (33). However, some find the PRIME-MD to be too time consuming, which prohibits its use in clinical settings. More recently, the patient-rated screening segment of the PRIME-MD, the PRIME-MD Patient Health Questionnaire (PHQ), has been validated alone (34), and it offers a more feasible approach to screening for psychiatric disorders, including GAD.

COURSE

Although the duration of symptoms specified in the diagnostic criteria for GAD has increased over time, studies of the long-term course of GAD have found a mean duration of illness longer than 6 months, and with a generally chronic course. In the ECA study, for example, 40% of those with GAD had the diagnosis for more than 5 years (35). A prospective longitudinal clinical study, the Harvard-Brown Anxiety Research Program (HARP) (36), similarly found GAD to be persistent. After 2 years, 60% of subjects still had active GAD. At 5 years, 66% of this group had only had partial remission or no remission of their GAD. In

the ECA study, of those whose GAD did remit, 27% relapsed within 3 years (35).

Several follow-up studies have examined the course of GAD and found that the presence of a comorbid psychiatric disorder or a personality disorder predicts poor outcome (37, 38). The HARP study examined quality-of-life variables over 5 years (35) and found that a lower overall satisfaction with life and a poorer quality relationship with a spouse or other relative predicted a lower likelihood of remission from GAD. While the reasons for the high chronicity of GAD symptoms over time are complex, they likely include a combination of factors such as inadequacy of identification and treatment of the disorder as well as an interaction of life stressors and comorbidity with GAD.

BURDEN AND IMPACT ON QUALITY OF LIFE

GAD is associated with substantial reductions in quality of life and impairment in role functioning. In the National Comorbidity Survey, distress and role impairment among respondents with GAD were determined on the basis of three questions: whether the disorder ever interfered a lot with their life and activities, whether they ever sought professional help for the disorder, and whether they ever took medication for the disorder (7). Eighty-two percent of those with GAD and a co-occurring disorder answered yes to one of these questions. Of those with pure GAD, 59% answered yes. This suggests that although GAD may be more impairing in the presence of comorbidity, GAD is itself associated with significant impairment.

GAD-associated disability was also examined in the WHO Collaborative Study on Psychological Problems in General Health Care, which pooled data from 14 countries. The study included measurements of physical disability, number of disability days per month (i.e., days when the respondent was unable to carry out his or her usual daily activities), and interviewer-rated occupational role functioning (39). Thirty-eight percent of subjects with GAD had moderate or severe impairment of occupational role functioning, with a mean of 6.3 disability days per month. In addition, individuals with "pure" GAD in an HMO setting have been found to have significantly poorer social functioning (40).

GAD has been shown to be at least as impairing as some medical disorders. The MacArthur Foundation's Midlife Development in the U.S. Survey (MIDUS), which studied more than 3,000 adults across the United States, examined the frequency of work impairment days (a combination of sick days or work-cutback days) associated with the 20 most common chronic health problems, including several psychiatric disorders. Individuals with GAD had more work impairment days (6 days per month) than those suffering from ulcers (5.8 days per month), asthma, diabetes, or arthritis (3.1 to 3.5 days per month) (41).

BIOLOGICAL UNDERPINNINGS

GENETIC STUDIES AND MOLECULAR BIOLOGY

Several family and twin studies have examined the potential role of genetics in the etiology of GAD, although more data are needed for a full understanding of the genetics of GAD. Two family studies of patients with GAD and their first-degree relatives (parents, siblings, and children) measured the frequency of the disorder in comparison with control families. The first study found that about 20% of first-degree relatives of patients also had GAD, compared with about 4% of those in control families (42), indicating a fivefold elevation in risk for the disorder in family members (relative risk=5.6). The second study also suggests a modest heritability of GAD, finding the disorder in 22% of first-degree relatives of those with anxiety disorders (43). A recent meta-analysis of family and twin studies (44) reported that family members of patients with GAD were six times more likely than others to have GAD themselves (Mantel-Haenszel summary odds ratio=6.1, 95% CI=2.5–14.9), further supporting a moderate familial aggregation of GAD.

Twin studies of GAD have been conducted, using the equal-environments assumption to examine differences between monozygotic and dizygotic twins to separate genetic and environmental influences. No adoption studies are available, however. In a study of 63 monozygotic twins and 81 dizygotic twins, 21% of monozygotic twins both had GAD, whereas 13% of the dizygotic twins did (45). A meta-analysis of several twin studies used structural equation modeling (44) and found that approximately 32% of the variance in liability to GAD was attributable to additive genetics, providing additional evidence that GAD is a moderately heritable disorder.

The data supporting a partial genetic transmission of GAD have prompted researchers to search for genetic markers that are correlated with the disorder. As with other anxiety disorders, promising candidate genes for study include those that influence norepinephrine and serotonin neurotransmission as well as gamma-aminobutyric acid (GABA) and corticotropin-releasing factor. One gene of interest is the serotonin transporter gene located on

chromosome 17q. A polymorphism of the second intron of the serotonin transporter gene, which contains multiple copies of the variable-number-tandem-repeat element (STin2.12), has been associated with depression (46). This same polymorphism was identified at significantly higher rates in individuals with GAD compared with control subjects in a study of 39 patients (47). Larger studies are needed to confirm and expand on these findings.

GABA is the brain's main inhibitory neurotransmitter, and the GABA receptor system has been an important focus of research in understanding the neurobiology of anxiety disorders. Benzodiazepines, which have their effect at the GABA receptor, are well established as anxiolytic agents. Recent advances in molecular biology techniques have allowed direct scientific exploration of the role of GABA in animal models. One study, for example, generated mice heterozygous for the gamma 2 subunit of the $GABA_A$ receptor, which causes partial impairment of $GABA_A$ receptor function (48). When presented with a free-choice exploration task, these genetically altered mice were less likely than wild-type mice to explore new areas of a compartment. In addition, when exposed to ambiguous stimuli, the mice with impaired $GABA_A$ receptor function were more likely to show a freeze response, indicating a greater likelihood of interpreting ambiguous situations as threatening. The behavioral inhibition seen in these mice was normalized by the use of diazepam to partially restore GABAergic function. These experiments suggest that $GABA_A$ receptor impairment may contribute to anxiety-related behavior.

Although emerging data support a role for genes and biological factors in the etiology of GAD, the disorder's moderate heritability reflects a small influence compared with the classic model of genetically inherited diseases. Thus, although genes may play a part, and the genetics of GAD are likely complex, other individual and environmental factors appear to contribute significantly to the development of GAD.

NEUROIMAGING

Neuroimaging offers a potentially powerful technique for examining the biology of GAD, although available data are limited. Neuroimaging studies of anxiety have generally focused on delineating fear circuitry, which corresponds to fear-based disorders such as panic disorder, social phobia, and posttraumatic stress disorder (49). GAD has been conceptualized as a worry-based rather than a fear-based disorder. There are, however, a small number of suggestive preliminary findings derived from neuroimaging studies of GAD.

A positron emission tomography (PET) study measuring cerebral glucose use in various parts of the cortex in 18 subjects with GAD found elevated metabolism in the left inferior occipital lobe, right posterior temporal lobe, and right precentral gyrus, compared with control subjects during a passive viewing task (50). Subjects also performed an active vigilance task, which resulted in activation of the basal ganglia. After a benzodiazepine was administered, glucose metabolism was reduced in the cortex, limbic system, and basal ganglia, compared with normal controls. These findings suggest that the basal ganglia may be implicated in GAD.

Increased activation in the occipital lobe has been postulated to be related to the symptom of hypervigilance observed in some patients with anxiety. A study of GAD with single photon emission tomography (SPET) and a specific benzodiazepine receptor radioligand (51) showed that benzodiazepine receptor binding of the radioligand was significantly decreased in the left temporal pole in the brains of patients with GAD compared with normal controls. This is consistent with the known regional distribution of benzodiazepine receptors, which are part of the receptor system of the inhibitory neurotransmitter GABA. These findings suggest that there may be an abnormality in the functioning of the GABA receptor system, causing the experience of anxiety. While the rapidly advancing technology of neuroimaging holds promise for future work delineating the neurobiology of worry, as distinguished from fear, and of GAD in particular, this neurobiology is not yet well understood.

OTHER BIOLOGICAL STUDIES

Phenotypic markers of anxiety disorders have also been examined. For example, while there is greater evidence for autonomic dysregulation in other anxiety disorders, such as panic disorder, one study of 34 subjects with GAD found lower vagal tone in individuals with GAD compared with control subjects, as measured by shorter heartbeat interbeat intervals and reduced interbeat variability with spectral analysis (52). Biological correlates of GAD have also been examined via studies of neurotransmitter levels and receptor function, and via levels of neurohormones and peptides. For example, abnormally low levels of peripheral benzodiazepine receptors (pBR) as well as pBR mRNA have been detected in lymphocytes of people with GAD (53). These levels returned to normal after the patients were treated with a diazepam-related compound for

two months, suggesting that the abnormally low levels of pBRs seen at baseline may be a state-related biological abnormality that may be altered with treatment. The return to normal pBR levels was also correlated with the amount of clinical improvement, and normal levels remained even 1 month after discontinuation of the benzodiazepine.

The monoamine neurotransmitters serotonin and norepinephrine have been of interest in research on anxiety disorders because medications that affect these systems are effective in the treatment of anxiety disorders. Several methods of examining monoamine neurotransmitters have been used in studying GAD, including measurements of neurotransmitter plasma levels, metabolite levels in urine, and challenge studies with antagonists. However, these studies have not produced a clear picture of the role of serotonin and norepinephrine in the underlying neurobiology of GAD. For example, one study reported elevated plasma levels of norepinephrine and decreased alpha$_2$-adrenoreceptor function and concluded that norepinephrine activity is elevated in GAD, causing receptor down-regulation (54). Other investigators, however, have not had the same finding (55, 56).

The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in several anxiety disorders. The main stress hormone, cortisol, appears to be elevated in patients with GAD (57) as well as in those with other anxiety disorders (58, 59). Corticotropin-releasing factor (CRF), which is found in highest concentrations in the hypothalamus, has been shown to cause anxiety in animals when injected directly into the cerebral ventricles or the locus ceruleus (60, 61). Increased anxiety-like behavior is also seen in transgenic mice that overexpress CRF (62). Interest in the HPA axis and anxiety, and the demonstrated association of CRF abnormalities and anxiety seen in preclinical animal models of anxiety, have supported continuing investigation of a potential role for CRF antagonists in the treatment of anxiety disorders.

PHARMACOTHERAPY

BENZODIAZEPINES

Benzodiazepines remain the most widely used medication for GAD, according to a survey of 73 international experts in the pharmacotherapy of anxiety and depression (63). Benzodiazepines have been shown to work by potentiating the effects of GABA$_A$ receptors, which are inhibitory, via the entry of chloride ions into the cell. The cell is then hyperpolarized, reducing its ability to generate an action potential.

The various benzodiazepines differ in pharmacodynamic properties such as half-life, which influence the rapidity of onset, the frequency of dosing, and the likelihood of "interdose rebound." For example, short-acting agents such as alprazolam can cause increased anxiety symptoms between doses, a phenomenon that has been conceptualized as "mini-withdrawal" or "interdose rebound" (64). The benzodiazepines also differ in their level of hepatic metabolism versus renal excretion, which is most relevant for patients with comorbid medical illnesses that may influence renal or liver function. For example, most benzodiazepines are first metabolized by hepatic oxidation, then glucuronidation (65). Lorazepam and oxazepam undergo only hepatic glucuronidation and thus are preferable for patients whose hepatic function is compromised. Benzodiazepines with a long half-life may accumulate in patients with slow clearance, such as elderly patients and patients with liver disease, and this may result in excessive sedation (65).

Although some of the benzodiazepines have more data supporting their use in treating the anxiety disorders (e.g., clonazepam, diazepam, lorazepam, and alprazolam), as a class the benzodiazepines have roughly equivalent efficacy for anxiety (66). According to naturalistic data from the 5-year Harvard-Brown anxiety disorders (HARP) study, the drug most frequently used by individuals with GAD is alprazolam (31%), followed by clonazepam (23%). Although many studies have demonstrated efficacy for the benzodiazepines in the treatment of GAD (67–69), some data suggest that after initial improvement, the effect of benzodiazepines is not significantly different from placebo, and thus benzodiazepines may not be helpful in long-term treatment (70–72). For example, a study of diazepam (at a maximum dose of 40 mg), buspirone, and placebo found no significant difference in efficacy at 4 weeks (73). There is also some evidence that benzodiazepines may provide relief from somatically based symptoms rather than psychologically based ones. A study at Johns Hopkins University comparing alprazolam and imipramine in the treatment of GAD found that although patients who received both medications improved, alprazolam was more effective in attenuating the somatic symptoms of anxiety, whereas imipramine was more effective for psychic symptoms (74). It should be noted that some (75) but not all (76, 77) studies have reported that benzodiazepines worsen depression. In either case, monotherapy with a benzodiazepine is not effective for depression, which is commonly comorbid with

GAD. Monotherapy with benzodiazepines is thus contraindicated in the presence of depression. Further research is needed to determine the optimal treatment of comorbid GAD and depression, although benzodiazepines are often clinically a useful adjunct to primary antidepressant treatment in this setting.

Benzodiazepines are favored for their rapid action, but they may cause undesirable side effects. The most common are sedation, motor impairment, memory problems, and other cognitive impairment. Other concerns involve the physiologic dependence associated with regular use of these agents and the potential for abuse, particularly in populations with a history of substance abuse. Although a recent longitudinal study of patients using benzodiazepines suggested that a small proportion (1.6%) of patients escalate the dose over time (78), long-term use of benzodiazepines does carry the risk of dependence and is not entirely free of complications. For example, chronic use carried into old age may increase the risk of falls (79). Finally, discontinuation of benzodiazepines can be difficult for some patients, who may experience symptoms of withdrawal, symptom rebound, or even relapse. In such instances, a slow taper schedule with close monitoring is recommended. For patients who have difficulty tapering, data from panic disorder studies suggest that cognitive behavior strategies may be helpful in benzodiazepine discontinuation (80).

ANTIDEPRESSANTS

Tricyclic antidepressants. Clinical studies suggest that tricyclic antidepressants are at least as effective as benzodiazepines in the treatment of GAD (72, 81, 82), but with a slower effect. As noted above, results from one study suggest that tricyclics have a greater impact on the psychic symptoms of anxiety rather than somatic symptoms or hyperarousal (74). The most common side effects of tricyclic antidepressants are anticholinergic effects (dry mouth, blurred vision, and constipation), orthostatic hypotension, edema, sexual side effects, and weight gain. In addition, there is an increased risk of QT interval prolongation and cardiac conduction delay, especially in patients with preexisting heart disease or conduction abnormalities, which could in turn cause heart block (83). Torsades de pointes and sudden death are also associated with QT prolongation (83). Concern over the potential lethality of overdose with tricyclic antidepressants has limited their use for patients who are at high risk of suicide (84). With the availability of better-tolerated and safer antidepressants, such as the selective serotonin reuptake inhibitors, tricyclics are no longer considered first-line pharmacotherapy for the anxiety disorders.

SSRIs. Selective serotonin reuptake inhibitors (SSRIs) have become the first-line options for pharmacotherapy for GAD as well as other anxiety disorders because of their tolerability and safety profiles. Data from randomized controlled trials support their clinical efficacy in the treatment of GAD. Paroxetine has been found to be safe and effective in several large treatment trials. In an 8-week multicenter trial of 324 patients with GAD, for example, paroxetine flexibly dosed at 20–50 mg/day was significantly more effective than placebo in reducing GAD symptoms as well as in improving social functioning (85). A study comparing paroxetine, imipramine, and a benzodiazepine found a similar efficacy for paroxetine and imipramine, with both antidepressants superior to the benzodiazepine (81). This study supports the preferential use of SSRIs over benzodiazepines as first-line pharmacotherapy for GAD.

Accruing evidence also indicates that improvement from antidepressant treatment of GAD extends beyond the short term. Paroxetine, for example, has been shown to produce a continued benefit with longer-term use and to reduce the rate of relapse compared with discontinuing the drug: in a large, 32-week randomized double-blind discontinuation study, 73% of those on continued medication achieved remission by week 32, whereas the risk of relapse was five times higher for patients given placebo (86). The longer-term use of SSRIs for GAD may also result in improvement in some temperament and character variables such as "self-directedness" and "cooperativeness," indicative of long-term benefits in social function and well-being (87). Paroxetine has Food and Drug Administration (FDA) approval for GAD.

Substantial data also support the safety and efficacy of escitalopram for GAD, and in December 2003 the drug received FDA approval for GAD. In double-blind, placebo-controlled studies of escitalopram with some 580 subjects with GAD, significant improvement compared with placebo was reported in anxiety symptoms after 8 weeks (88, 89). The most frequent side effects of escitalopram are headache, nausea, somnolence, insomnia, and ejaculation disorder. A 9-week double-blind, placebo-controlled study of sertraline given to 22 children 5–17 years old suggested that SSRIs are probably also effective for GAD in children (90). A small retrospective case observation study of 13 GAD patients treated with citalopram led to improvement or partial improvement in GAD symptoms (91). These data support the efficacy of SSRIs for GAD, and many clinicians believe that SSRIs as a class have

equivalent efficacy for GAD. Data supporting this notion, however, are not available.

SSRIs are commonly recommended as the first-line treatment for anxiety disorders, although side effects sometimes hinder their use. Side effects occur most commonly when SSRIs are first started, as patients await the onset of beneficial effects. This can be a particular problem for the subset of anxious patients who already fear their physical anxiety symptoms and may be more sensitive to side effects. Common side effects of SSRIs include nausea, sedation, jitteriness, insomnia, and sexual side effects such as decreased libido. Since benzodiazepines provide a more rapid initial relief of symptoms and do not have the problematic side effects listed above, and because SSRIs and benzodiazepines have different mechanisms of action but converging effects, a common strategy is to combine these medication classes. One option is to use a benzodiazepine during the first several weeks of SSRI treatment to help with the side effects of SSRI initiation and to provide early symptomatic relief. The benzodiazepine can then be tapered while the antidepressant is continued. This strategy is supported by findings from a recent study of panic disorder suggesting earlier benefit from the combination of an SSRI and a benzodiazepine compared with an SSRI alone, but no difference in efficacy by 12 weeks, whether or not the benzodiazepine was tapered off or continued beyond the first 5 weeks (92).

Novel antidepressants. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), also has FDA approval for GAD. Its safety and efficacy are supported by several large randomized placebo-controlled trials. In a fixed-dose study of extended-release (XR) venlafaxine (75 mg, 150 mg, and 225 mg/day), venlafaxine was more effective than placebo and more effective than buspirone (93, 94). A later study evaluated venlafaxine XR in treatment up to 28 weeks and found long-term efficacy (95). Side effects from venlafaxine XR include nausea, dry mouth, somnolence, dizziness, sweating, constipation, and decreased appetite.

BUSPIRONE

Buspirone, the only azapirone available in the United States, has FDA approval for the treatment of GAD. The drug is thought to act as a partial agonist to the presynaptic serotonin 1A receptor (98). Efficacy studies of monotherapy with buspirone for the treatment of anxiety have been mixed. At least 15 double-blind, placebo-controlled trials of buspirone have been conducted, typically comparing buspirone with a benzodiazepine, placebo, or both (73, 99–112). Ten of these studies found some evidence that buspirone was more effective than placebo, but none found it to be more effective than a benzodiazepine, and in some cases it was found to be clearly less effective (104, 108). The effects of buspirone generally occur by 2 to 3 weeks, which is slower than benzodiazepines. The results of one study suggest that benzodiazepines may be more helpful for somatic symptoms, and buspirone for psychic symptoms of anxiety (such as cognitive and interpersonal symptoms) (100). Common side effects of buspirone include nausea, decreased appetite, and dizziness. Although somewhat less effective, buspirone is better tolerated than benzodiazepines and is free of abuse liability and physiologic dependence. Thus, buspirone provides a safe treatment option for patients with GAD who are at risk of substance abuse or are unable to tolerate benzodiazepines or antidepressants.

Buspirone may be most useful as an adjunctive medication, added to an SSRI for the treatment of both depression and anxiety disorders. Some data suggest that buspirone is an effective augmentation strategy in social phobia and panic disorder (113, 114). To date, however, there are no published data from trials of adjunctive buspirone for GAD. One hypothesis about the mechanism by which buspirone augments SSRI efficacy is that buspirone's presynaptic receptor effects, which are not dependent on serotonin levels, may result in slowed neuronal impulses and thereby allow serotonin levels to replete in the synapse (98).

OTHER PHARMACOTHERAPIES

A number of novel agents hold some promise as pharmacotherapy treatment options for GAD. Pregabalin is a lipophilic GABA analogue with a novel, non-GABA-ergic mechanism of action that is currently under development as an anticonvulsant agent, an analgesic for neuropathic pain, and an anxiolytic, but it is not yet available in the United States (115). Large, short-term double-blind studies of patients with GAD who have been treated with pregabalin, lorazepam, or placebo (116, 117) support the safety and efficacy of pregabalin compared with placebo, with benefits noted as early as the first week. Pregabalin appears to have comparable efficacy to benzodiazepines but without physiologic dependence. The most common reported adverse events with pregabalin are somnolence and dizziness.

Tiagabine, a selective GABA reuptake inhibitor that is currently available as an anticonvulsant, may also have anxiolytic effects. An open-label trial of

tiagabine with 40 patients with GAD (118) showed reductions in anxiety, comorbid depressive symptoms, and sleep difficulties. The most common side effects of tiagabine are sedation, dizziness, poor coordination, nausea, and tremor. Hydroxyzine, an antihistamine, has also been shown to be effective and well tolerated in the treatment of GAD (119). A recent 12-week trial conducted in France with 334 patients with GAD compared hydroxyzine, the benzodiazepine bromazepam, and placebo. Hydroxyzine and bromazepam were equally superior to placebo, although bromazepam was associated with more drowsiness (120).

In addition to traditionally prescribed pharmacotherapies, there appears to be significant interest in the U.S. population in alternative or complementary medicine approaches to the treatment of anxiety and depression. For example, in a recent survey, 57% of 2,055 respondents who reported anxiety attacks had tried complementary and alternative therapies (121). A few of these alternative agents have undergone preliminary assessment for use in treating GAD, but the data are far from definitive. In a small Brazilian study, for example, valerian extract, diazepam, and placebo all resulted in significant reductions in total anxiety scores, although only the groups taking diazepam and valerian extract had a significant reduction in the psychic symptoms subset (122). A double-blind, placebo-controlled study of homeopathy with 44 patients with GAD found no significant differences between the homeopathy and placebo groups after 5 weeks and 10 weeks of treatment (123).

In summary, several pharmacologic treatment options for GAD are available. SSRIs and venlafaxine are the most well studied, with large placebo-controlled trials supporting their safety and efficacy in the treatment of GAD. Benzodiazepines and buspirone may be particularly useful for augmentation of other pharmacotherapy, either to speed the onset of beneficial effects or to boost response. Decisions about pharmacotherapy for an individual patient should include consideration of comorbid psychiatric and medical disorders, prior treatment experiences, family history of response, and the individual's symptom characteristics and life situation.

PSYCHOSOCIAL TREATMENTS

Several forms of psychotherapy are used in treating GAD. Cognitive behavior therapy has received the most formal study, and the combination of psychotherapy and pharmacotherapy is a little-studied but clinically common and promising option.

PSYCHODYNAMIC PSYCHOTHERAPY

Although psychodynamic psychotherapies are commonly used and may be helpful for patients with GAD, little systematic research has been done on traditional psychoanalytic psychotherapy for GAD, in part, no doubt, because of the methodologic difficulties of studying a lengthy and less directed treatment in which the focus varies greatly from individual to individual. It is noteworthy that Freud's description of anxiety neurosis included the core symptoms of GAD. Traditional psychodynamic psychotherapy for anxiety disorders involves a collaboration between therapist and patient to uncover the patient's underlying intrapsychic conflicts. Some research has suggested that patients with GAD tend to have conflictual feelings about their caregivers and have a relative lack of childhood memories. Patients with symptoms of GAD have also reported oscillating feelings toward caregivers, including anger and enmeshment (124).

Although supported by only one comparative study (125), cognitive therapy approaches may be more effective than analytic psychotherapy in relieving the symptoms of GAD. In the study, 110 patients with GAD were randomly assigned to cognitive therapy or analytic psychotherapy. Six months later, 60% of the patients who received cognitive therapy scored in the normal range of functioning, compared with 20% of those receiving analytic psychotherapy. One year later, overall improvement was "moderate" to "very considerable" in 45% of the analytic psychotherapy group, compared with 71% in the cognitive therapy group; notably, patients in both groups had a high frequency of contact with their therapists, defined as 16–20 contacts over a 6-month period (126). While some research has supported the efficacy of brief dynamic therapy for the treatment of panic disorder (127), data are needed for GAD. As with pharmacotherapy, however, selection of psychotherapy is complex and should take into account the patient's specific needs, life stressors, prior treatment experience, and comorbid disorders.

COGNITIVE BEHAVIOR THERAPY

Cognitive behavior therapy (CBT) is an effective treatment for fear- and avoidance-based anxiety disorders, such as specific phobias and panic with agoraphobia. Although cognitive therapy approaches for GAD are already supported by a more extensive literature than psychodynamic psychotherapy, CBT for the disorder is still under refinement. Cognitive behavior strategies for GAD developed somewhat later than those for other anxiety disorders, partly because of the shift in diag-

nostic criteria over time, but also because the more diffuse experience of anxiety in GAD is more difficult to target with CBT. For example, while CBT for a phobia might involve exposure to a feared and avoided object or situation, the worry-based anxiety triggers for GAD are less concrete and frequently shift. Psychosocial therapies were thus initially focused on relaxation methods to aid in coping with anxiety generally. Later treatment developments have included strategies to identify and address thought patterns and characteristic responses in GAD (128).

As research has progressed in the psychotherapy of GAD, more specific psychological features of GAD have been identified as targets for cognitive behavior work. For example, subjects with GAD have been found to be more likely to interpret neutral stimuli as negative or threatening. In a study that presented words that have the same pronunciation but different meanings and spellings with either a threatening or neutral meaning (i.e., "flu" and "flew"), subjects with GAD were more likely than control subjects to select the threatening words (129). This phenomenon supports other research suggesting that patients with GAD have an "attentional bias" (130) toward threatening stimuli, which may then become distracting to the individual. In everyday life, an example might be a news report about unemployment levels or an outbreak of illness. Individuals with GAD would be more likely to attend to this information and worry that they or those close to them might lose their jobs or become ill, to an extent beyond that justified by their specific life circumstances. This idea of distraction by threatening stimuli was tested in a study that asked subjects to press a button to indicate the location of various words on a computer screen (130); the difference in response times to words on the screen that were either physically or socially threat-related (e.g., "choking," "emergency," and "ashamed") compared with neutral words ("incline" and "bracelet"), was greater for subjects with GAD than for control subjects. While it has been hypothesized that patients with GAD are more likely to consider ambiguous events as dangerous and thus view more events as potentially dangerous, this hypothesis has not been formally tested (124).

Some of these cognitive styles have been the target for change in CBT. For example, patients' negative interpretations of neutral events can be systematically evaluated and questioned. Similarly, the overestimation of the likelihood of negative outcomes occurring, even when negative outcomes are a possibility, can also be delineated and addressed. The therapist and the patient work together to identify dysfunctional beliefs and automatic thoughts that underlie the negative interpretations and work toward alternatives to these beliefs and thoughts (128). Another approach might target exposure to the focus of the worrying, which has been conceptualized as a form of avoidance, resulting in a focus on the future rather than the present. In some cases, the patient may be led through an exposure exercise in which he or she is asked to create vivid imagery of the feared outcome, in tandem with the application of coping strategies (131).

Recent work suggests a role for additionally aiding patients with emotion regulation skills (132). Mindfulness strategies may also help patients shift their patterns of behavior toward a more present-focused approach (133). Mindfulness may be a component of relaxation training, which has also been employed for GAD. This type of treatment might start with psychoeducation about anxiety in general, followed by instruction in progressive muscle relaxation. After developing skill in self-relaxation, the patient can apply it as needed during moments of increased worry and anxiety (134).

Research has suggested that CBT techniques can be effective for GAD. Because multiple, nondefinitive studies of CBT for GAD have been published, meta-analytic approaches have been used to help summarize the data. One meta-analysis included seven studies comparing CBT to either medication (diazepam), pill placebo, nondirective therapy, or a waiting list control (135). The number of treatment sessions ranged from six to 16. In all seven studies, CBT was more effective than waiting list or placebo, with a large average effect size (1.54) for CBT, reflecting a substantial reduction in anxiety. Comparison between CBT and nondirective therapy was less clear and was difficult to sort out because of methodological factors.

Another meta-analysis examined 11 studies that used various treatment approaches for GAD (128). CBT was repeatedly associated with statistically and clinically significant change at the study's end as well as up to 1 year later. Less clear is precisely which elements of CBT confer the treatment effect. This meta-analysis found that the best long-term improvement occurred when multiple components of the therapy were used, such as relaxation training to address physical symptoms such as muscle tension and cognitive restructuring to address cognitive features of GAD, such as excessive worry.

Finally, a meta-analysis of 35 studies published or presented between 1974 and 1996, with 61 separate treatment interventions, found an overall effect size of CBT for anxiety of 0.7, which was not significantly different from that of pharmacother-

apy (effect size=0.6). Patients who received CBT also had benefited from a reduction in symptoms of depression as well as the long-term maintenance of treatment gains. These results contrast with some loss of treatment gains seen for patients who responded to pharmacotherapy for GAD but then discontinued medication (136). These findings suggest that even after treatment discontinuation, CBT provides a lasting benefit, probably to a greater extent than pharmacotherapy.

CONCLUSIONS

GAD is a chronic anxiety disorder that is associated with significant impairment in work and social functioning and is often comorbid with other medical and psychiatric disorders. Despite its substantial impact, GAD remains underdiagnosed and undertreated in the primary care setting, strongly indicating the need for more effective and simpler screening by clinicians.

The validity of GAD as a distinct diagnostic entity has been questioned historically. Recent research comparing GAD with other disorders, however, has provided compelling evidence that GAD constitutes a distinct disorder. Genetic studies indicate that GAD has moderate heritability, and neurobiological research implicates distinct abnormalities in several domains, including the serotonin transporter gene and benzodiazepine receptors.

A number of safe and effective treatment options are available for patients with GAD. Psychosocial treatments such as CBT and relaxation therapy are effective, both alone and in combination with medication. Pharmacotherapy options include SSRIs, venlafaxine, benzodiazepines, and other agents; optimal pharmacotherapy is determined by individual needs and the presence of comorbid disorders. Further research is needed to explore treatment algorithms for patients whose anxiety is refractory to initial treatment interventions. Research examining novel pharmacotherapies and refining psychosocial approaches to the treatment of GAD is under way and promises to provide additional treatment options to improve the long-term outcome for patients with GAD.

DISCLOSURE OF UNAPPROVED OR INVESTIGATIONAL USE OF A PRODUCT

APA policy requires disclosure by CME authors of unapproved or investigational use of products discussed in CME programs. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by the scientific literature and clinical experience. This article discusses the efficacy of sertraline, pregabalin, tiagabine, hydroxyzine, and valerian extract in treating generalized anxiety disorder.

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