CLINICAL PRACTICE

Generalized Anxiety Disorder

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

During a routine visit, a 59-year-old woman, who describes herself as a lifetime "worrier" and has a family history of depression, reports having restless sleep, muscle tension, and fatigue. Recently, her anxiety has intensified about her children, her job, and her health, and it is having a negative effect on her family and work life. How should she be treated?

THE CLINICAL PROBLEM

Anxiety disorders are the most prevalent psychiatric conditions in the United States aside from disorders involving substance abuse.[1] Generalized anxiety disorder has a lifetime prevalence of 5 percent. The criteria for diagnosis, as specified by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, are summarized in Table 1.[2] The onset is usually before the age of 25 years, and the incidence in men is half that in women. Untreated, the typical course is chronic, with a low rate of remission and a moderate recurrence rate.[3]

Risk factors for generalized anxiety disorder include a family history of the condition, an increase in stress, and a history of physical or emotional trauma.[4,5] An association has also been reported between smoking and anxiety, and the risk of generalized anxiety disorder among adolescents who smoke heavily is five to six times the risk among nonsmokers.[6] Traits such as nervousness and social discomfort may predispose people to both nicotine dependence and anxiety.[7] Medical illnesses are often associated with anxiety.[8] For example, generalized anxiety disorder occurs in 14 percent of patients with diabetes.[9]

COEXISTING PSYCHIATRIC ILLNESSES

Major depression is the most common coexisting psychiatric illness in patients with generalized anxiety disorder, occurring in almost two thirds of such patients. Panic disorder occurs in a quarter of patients with generalized anxiety disorder, and alcohol abuse in more than a third.[1,10] Studies of twins suggest a shared genetic propensity to both generalized anxiety disorder and major depression,[11] and a recent report suggests that a genetic variant of the serotonin-transporter gene may predispose people to both conditions.[12] In prospective studies, anxiety almost always appears to be the primary disorder and to increase the risk of depression.[13] Patients who have generalized anxiety disorder along with coexisting psychiatric illnesses have more impairment, seek more medical attention, and have a poorer response to treatment than those without coexisting illnesses.[14]

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STRATEGIES AND EVIDENCE

DIAGNOSIS

Patients with generalized anxiety disorder often have physical symptoms, and it may be difficult to distinguish the symptoms from those of medical illnesses that are associated with anxiety.[15] Factors suggesting that anxiety is the symptom of a medical disorder include an onset of the symptoms after the age of 35 years, no personal or family history of anxiety, no increase in stress, little or no avoidance of anxiety-provoking situations, and a poor response to antianxiety medication.[16] A physical cause should be suspected when anxiety follows recent changes in medication or accompanies signs and symptoms of a new disease.

In evaluating patients for generalized anxiety disorder, practitioners should routinely consider medical conditions (e.g., cardiac, pulmonary, neurologic, or endocrine illnesses, including hyperthyroidism), drug use (e.g., cocaine and other stimulants, such as caffeine), drug withdrawal (e.g., cessation of the use of alcohol, opiates, or benzodiazepines), and both prescribed and over-the-counter medications (e.g., corticosteroids, sympathomimetics, and herbal medicines, such as ginseng).[10,15]

Before making a diagnosis of generalized anxiety disorder, practitioners should take a history and perform a physical examination in order to rule out medical causes of anxiety. Laboratory testing should be guided by the clinical presentation. The cost-effectiveness of specific laboratory testing is uncertain, but given the increased prevalence of generalized anxiety disorder among patients with hyperthyroidism, measurement of thyrotropin is reasonable.[17]

Other psychiatric disorders that may be misdiagnosed as generalized anxiety disorder require consideration. Whereas generalized anxiety disorder is defined as worry that is present most of the time for at least six months, panic disorder is characterized by recurrent panic attacks, followed by at least one month of persistent anxiety about having more attacks. Obsessive–compulsive disorder is manifested as intrusive thoughts and ritualistic actions; posttraumatic stress disorder as avoidance, numbing, and hyperarousal; social phobia as severe anticipatory anxiety accompanying social situations; and somatization disorder as multiple physical symptoms in the absence of or out of proportion to underlying disease.

ASSESSMENT OF DEPRESSION AND SUICIDE RISK

When generalized anxiety disorder complicates major depression, there is an increased risk of suicide.[18] Patients should be asked about depressive symptoms, including suicidal ideation. If answers suggest that the patient is at risk for suicide, a psychiatric evaluation should be performed as soon as possible.

THERAPY

PHARMACOTHERAPY

In part because depression is frequently associated with generalized anxiety disorder, antidepressant agents are often used as first-line agents for treating the latter condition.[19] Commonly used agents and their doses and side effects are summarized in Table 2.

Tricyclic Antidepressants

Tricyclic agents are effective for treating patients who have generalized anxiety disorder alone or in association with depression.[20,21] In one randomized, controlled trial, the response to imipramine was significantly greater than the response to placebo, with an improvement in symptoms that was more than 50 percent at eight weeks.[21] When first initiated, tricyclic agents can cause jitteriness and insomnia, and thus treatment should be initiated at half the usual dose. Tricyclic therapy can be hampered by side effects, which may reduce a patient's adherence to treatment (Table 2).

Selective Serotonin-Reuptake Inhibitors

The efficacy of selective serotonin-reuptake inhibitors (SSRIs) is similar to that of tricyclics, and SSRIs have a more favorable side-effect profile. In an eight-week, randomized, placebo-controlled trial involving 326 outpatients, those who received paroxetine (20 to 50 mg per day) had a significantly higher response rate (defined as much or very much improved, with a reduction in anxiety and better functioning) than those who received placebo (72 percent vs. 56 percent) and a significantly higher rate of remission, which was defined as minimal or no anxiety and no functional impairment (42 percent vs. 26 percent).[22] These results have recently been replicated.[23]

In a follow-up study, patients who had had a response to paroxetine in the 8-week trial were randomly assigned to continue to take paroxetine or to

Table 1. Diagnostic Criteria for Generalized Anxiety Disorder.*

The patient reports having 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).
The patient has difficulty in controlling worry.
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 previous 6 months): restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).†
The focus of the anxiety and worry is not confined to features of other types of psychiatric disorders (e.g., panic disorder, social phobia, obsessive–compulsive disorder, separation anxiety disorder, anorexia nervosa, somatization disorder, or hypochondriasis), and the anxiety and worry do not occur exclusively as part of post-traumatic stress disorder.
The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
The disturbance is not due to the direct physiological effects of a medication, substance abuse, 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.

* Adapted from the American Psychiatric Association.[2]
† Only one item is required in children.

take placebo for an additional 24 weeks.[24] The rate of relapse during this period was 11 percent for patients receiving paroxetine, as compared with 41 percent for those receiving placebo. Among the patients who continued to receive paroxetine, the rate of remission after six months (73 percent) was higher than the rate at the end of the eight-week study, a finding suggesting that a longer course of treatment increases the likelihood of remission.

Restlessness can occur with the initiation of SSRI therapy, so starting doses should be low. Paroxetine is the SSRI that has been studied most extensively for the treatment of generalized anxiety disorder, and it is approved by the Food and Drug Administration (FDA) for this indication, but other members of this class of medications, such as citalopram and escitalopram, have also been shown to have efficacy.[25,26] Concern about an increased risk of suicide among adults taking SSRIs, in particular, is not supported by a review of placebo-controlled studies involving a total of 48,277 depressed patients and nine antidepressants. The review showed no significant difference in suicide rates among the study groups.[27] However, the initiation of treatment with any antidepressant in a depressed patient requires monitoring for suicidal ideation and behavior.

Serotonin–Norepinephrine–Reuptake Inhibitors

Extended-release venlafaxine (Effexor XR), a serotonin–norepinephrine–reuptake inhibitor, is also approved by the FDA for treatment of both generalized anxiety disorder and depression and is effective when a patient has both conditions.[28] In a report of two double-blind, placebo-controlled trials of extended-release venlafaxine, the rates of response among patients with generalized anxiety disorder were 58 percent at eight weeks and 66 percent at six months (vs. 36 percent and 39 percent, respectively, for placebo).[29] Almost two thirds of patients who had no response to venlafaxine at eight weeks did have a response by six months. Remission rates for venlafaxine were 32 percent at eight weeks and 43 percent at six months (vs. 15 percent and 19 percent, respectively, for placebo). Caution is warranted with doses of extended-release venlafaxine that are greater than 225 mg per day, given the infrequent complication of sustained systolic hypertension, and in patients with a history of conduction disturbance or ventricular arrhythmias, given the risks of these complications with an overdose.

Duration of Therapy

Responses to the medications discussed above are expected within eight weeks when patients are receiving a therapeutic dose, although longer courses may yield more favorable results, particularly in those patients who have had partial responses. Although objective data on rates of relapse and remission with longer use of the medications are sparse, patients who have a response should generally be advised to continue taking the antidepressant for six months to a year. When a medication is ineffec-

Table 2. Psychopharmacologic Treatments for Generalized Anxiety Disorder.*

Medication	Class	Risk during Pregnancy†	Starting Dose‡	Titration Up	Target Dose‡	Side Effects§
Antidepressant anxiolytics						
Citalopram (Celexa)	SSRI	C	10 mg/day	10 mg after 7 days Maintain for 3–4 wk	10–40 mg	Nausea, vomiting, dry mouth, headache, somnolence, insomnia, sweating, tremor, diarrhea, sexual dysfunction, syndrome of inappropriate antidiuretic hormone, cytochrome P-450 2D6 substrate elevation due to enzyme inhibition (paroxetine especially; citalopram and escitalopram are not significant inhibitors), discontinuation effects (fatigue, dysphoria, psychomotor changes)
Escitalopram (Lexapro)	SSRI	C	10 mg/day	10 mg after 4 wk	10–20 mg	
Paroxetine (Paxil)	SSRI	C	10 mg/day	10 mg after 1–2 wk Maintain for 3–4 wk	10–40 mg	
Sertraline (Zoloft)	SSRI	C	25 mg/day	25 mg every 3–5 days	50–200 mg	
Venlafaxine (Effexor)	SNRI	C	25–37.5 mg/day	25 mg every 4–7days	50–75 mg 3 times/day	Nausea, somnolence, dizziness, dry mouth, nervousness, tremor, insomnia, constipation, sexual dysfunction, sweating, anorexia, blood pressure elevation, orthostasis, conduction defects, ventricular arrhythmias, discontinuation effects (fatigue, dysphoria, psychomotor changes); half usual dose used in moderate hepatic or renal impairment
Venlafaxine XR (Effexor XR)	SNRI	C	37.5 mg/day	37.5 mg every 4–7 days	75–225 mg	
Imipramine (Tofranil)	Tricyclic antidepressant	D	10 mg/day	20–25 mg every 7 days	50–200 mg	Orthostasis, conduction defects, ventricular arrhythmias, reflex tachycardia, anticholinergic effects, weight gain, potential lethality in overdose
Nortriptyline (Pamelor, Aventyl)	Tricyclic antidepressant	D	10 mg/day	10–25 mg every 7 days	20–150 mg	
Benzodiazepine anxiolytics						
Clonazepam (Klonopin)	Benzodiazepine	D	0.25 mg 2 times/day	0.25–0.5 mg every 4 days	0.5–2 mg	Sedation, ataxia, hypotonia, paradoxical agitation, memory changes, withdrawal syndrome
Lorazepam (Ativan)	Benzodiazepine	D	0.5 mg 2 times/day	0.5 mg every 4 days	1–4 mg	
Nonbenzodiazepine anxiolytic						
Buspirone (BuSpar)	Serotonin 1A agonist	B	5 mg 2 times/day	5 mg every 2–3 days	10–60 mg	Dizziness, headache, drowsiness, light-headedness, fatigue, nausea, insomnia, restlessness
Anticonvulsant anxiolytics						
Gabapentin (Neurontin)	Antiepileptic drug	C	100 mg 2 times/day	100 mg every 3 days	100–1800 mg	Somnolence, dizziness, ataxia, fatigue, nystagmus, nausea, dry mouth, constipation, peripheral edema, rhinitis, pharyngitis, visual changes, myalgia
Tiagabine (Gabitril)	Antiepileptic drug	C	2 mg 2 times/day	2–4 mg every 7 days	2–16 mg	Somnolence, nervousness, dizziness, tremor, abdominal pain, diarrhea, vomiting, asthma, pharyngitis

* Adapted from data from Pollack et al.,[10] Goldberg and Posner,[15] and Rosenbaum et al.[16] More information is available at the Web site of the Anxiety Disorders Association of America at www.adaa.org. SSRI denotes selective serotonin-reuptake inhibitor, and SNRI serotonin–norepinephrine reuptake inhibitor.

† The pregnancy-risk category is established by the FDA. B denotes that studies in animals do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women, or studies in animals have shown an adverse effect on the fetus, but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the findings in animals the possibility of fetal harm appears to be remote, if the drug is used during pregnancy. C denotes that studies in animals have shown that the drug has teratogenic or embryocidal effects, but there have been no adequate well-controlled studies in pregnant women, or no data are available in either animals or pregnant women. D denotes that positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.

‡ In perinatal and geriatric patients, approximately half the usual doses are used.

§ Serotonin syndrome can occur when SSRIs, SNRIs, tricyclic antidepressants, serotonin antagonist–reuptake inhibitors, monoamine oxidase inhibitors, and serotonin 1A agonists are used in various combinations.

tive or intolerable, switching to another agent in the same class or another class is reasonable, although this approach has not been extensively studied.[30]

Nonbenzodiazepine Anxiolytic Agents

Buspirone has been shown in double-blind, randomized, controlled trials to have efficacy in the treatment of generalized anxiety disorder.[31] It does not cause sedation, physical dependency, or withdrawal. However, it has no antidepressant effect, so it should not be used alone for anxiety with coexisting depression. A period of two to four weeks or longer is generally needed for a response.

Benzodiazepines

Double-blind trials have also shown the efficacy of benzodiazepines in treating generalized anxiety disorder, but the side effects are a concern (Table 2), particularly in elderly patients.[32,33] In one randomized trial comparing paroxetine, imipramine, and a benzodiazepine among nondepressed patients with generalized anxiety disorder, the benzodiazepine was the most effective of the three drugs during the first two weeks, but at eight weeks it was less effective than either antidepressant.[34]

With long-term benzodiazepine use (which is generally defined as use of a therapeutic dose for two months or more), patients may become physically dependent on the drug. However, addiction is infrequent and occurs mostly in patients at risk for substance abuse. To avoid withdrawal symptoms (which include seizures, hypersympathetic tone, and anxiety), the dose can be reduced gradually (e.g., a 1.0-mg reduction in the dose of lorazepam per week or a 0.5-mg reduction in the dose of alprazolam per week). Slow tapering is especially important for patients taking high-potency and short-acting benzodiazepines such as lorazepam and alprazolam. Alprazolam can be associated with a severe discontinuation syndrome, complicated by dysphoria and delirium. Switching to equipotent doses of long-acting clonazepam, with alprazolam available on an as-needed basis for one week, can make tapering easier.[10]

There are limited data to guide decisions about the duration of benzodiazepine therapy. In one study, among patients taking only diazepam for anxiety, discontinuation after six months resulted in a relapse rate of 63 percent within a year.[33] However, in most patients, tapering the dose as a means of gradual discontinuation is preferable to long-term use and is facilitated by treatment with anxiolytic antidepressants.[20]

Benzodiazepines can often be helpful as short-term treatment when antidepressants are initiated, since benzodiazepines rapidly relieve symptoms (whereas antidepressants typically take weeks to work) and also help alleviate the restlessness or nervousness sometimes associated with the initiation of antidepressant therapy. Benzodiazepines can be tapered over a period of several weeks after the anxiolytic effects of an antidepressant have taken hold. Nevertheless, in selected patients who have a relapse or cannot tolerate tapering of the dose in order to discontinue the drug, benzodiazepines may be used long term. A meta-analysis of nine studies of combined benzodiazepine–antidepressant treatment, including SSRIs and tricyclics, for coexisting anxiety and depression revealed that combined treatment was more likely than antidepressant therapy alone to reduce anxiety and depression and that it was associated with a lower dropout rate.[35]

PSYCHOTHERAPY

The most extensively studied psychotherapy for anxiety is cognitive behavioral therapy.[36] This therapy, which teaches patients to substitute positive thoughts for anxiety-provoking ones, usually involves 6 to 12 individual sessions at weekly intervals. Patients record their thoughts and feelings in diaries, noting situations in which they feel anxious and behaviors that relieve the anxiety. They also role-play scenes and rehearse responses to anxiety.

In one randomized, controlled study, 32 percent of patients in the group that received cognitive behavioral therapy had clinically significant improvement at three months, and 42 percent had clinically significant improvement at six months, whereas none of the patients in the control group had significant improvement at three months.[37] In a recent study that followed subjects from earlier randomized trials for 8 to 14 years, the condition of half of the patients who had an initial response to cognitive behavioral therapy remained markedly improved, approximately one third still had some improvement, and the rest had recurrent anxiety and disability.[38]

An alternative approach to cognitive behavioral therapy is applied relaxation therapy, in which the patient imagines calming situations to induce muscular and mental relaxation. One randomized, controlled trial comparing cognitive therapy with ap-

plied relaxation therapy showed no significant difference in improvement rates at one year.[39] Similarly, in a review comparing the outcomes of two studies of applied relaxation therapy with the outcomes of four studies of cognitive behavioral therapy, the response rates at six months were similar (52 percent for applied relaxation therapy and 41 percent for cognitive behavioral therapy).[40] Psychotherapeutic additions to cognitive behavioral therapy are being tried to improve the response rate, although the efficacy of these combined approaches is uncertain.[36]

AREAS OF UNCERTAINTY

RESISTANT GENERALIZED ANXIETY DISORDER

The optimal management of generalized anxiety disorder that is resistant to either psychotherapy alone or pharmacotherapy alone is uncertain.[41] If the patient's initial response to medication is inadequate, the dose should be increased as tolerated and then maintained for at least eight weeks. A patient's partial response to a medication may warrant a longer trial, given data that suggest further improvement with longer use. Combining psychotherapy and pharmacotherapy should also be considered, although data are lacking on whether the combination results in a better outcome than either approach alone.[42] The possibility of an underlying medical condition or a coexisting psychiatric illness should be reconsidered in resistant cases.[43]

Little research has been done on the effects of combining medications. For patients who have a partial response to one medication, combination treatment with antidepressants and benzodiazepines or buspirone, or augmentation with other agents, including anticonvulsants (e.g., gabapentin or tiagabine), may be helpful.[44,45]

PREVENTION

In one study, college students who were thought to be at risk for depression were randomly assigned to an eight-week cognitive behavioral workshop. At three years, they had fewer episodes of generalized anxiety than students who had undergone only an initial assessment.[46] More research on prevention is warranted.

SCREENING

Screening for generalized anxiety disorder is not routinely advocated in practice.[47] However, approximately 90 percent of patients with the condition answer "yes" to the question, "During the past four weeks, have you been bothered by feeling worried, tense, or anxious most of the time?" Some practitioners have supported using this question as a screening technique.[48]

PERINATAL MANAGEMENT

During pregnancy and the postpartum period, there is an increased risk that generalized anxiety disorder will develop or worsen. Psychotherapy may obviate the need for pharmacotherapy, but for severe anxiety (which may be associated with adverse obstetrical outcomes, including premature birth), medication may be necessary.[49]

There are no data from prospective controlled studies of antianxiety agents administered during pregnancy or lactation, and recommendations are based on observational data alone. Buspirone may be safer than some other medications during pregnancy. Benzodiazepines should not be used in the first trimester because of the risk of oral clefts. Use of benzodiazepines late in the third trimester may cause the floppy infant syndrome or neonatal withdrawal. Sedation may occur in breast-fed infants of women taking benzodiazepines.[49] If benzodiazepines are used perinatally, the rule is to use the lowest effective dose for the shortest period.

Although data are limited, SSRIs do not appear to be teratogenic. However, there have been reports of neonatal toxicity, such as early delivery, that was unrelated to the duration of fetal exposure and of low Apgar scores, including respiratory distress, in infants whose mothers were receiving the drugs in the third trimester.[49,50] When these medications are used prenatally, decisions about which drug to use may be based on apparent reproductive safety in practice (e.g., fluoxetine or citalopram) or on a low ratio of the cord drug concentration to the serum drug concentration, suggesting minimal fetal exposure (e.g., sertraline or paroxetine).[50,51] Nevertheless, concern has been expressed about the use of paroxetine near delivery because of reports of transient neonatal withdrawal symptoms, including respiratory distress, which in some cases has required intensive treatment.[49] Breast-fed infants are also exposed to antidepressants, and use of the lowest effective dose possible is advised during both pregnancy and lactation. A detailed discussion of the use of anxiolytic medications in pregnancy and lactation is beyond the scope of this review but is available elsewhere.[52,53] Ultimately, the risk of a medication should be weighed against the poten-

tial benefits of relief of serious illness and improved caretaking abilities, and decisions should be individualized.

GUIDELINES

There are currently no formal guidelines from U.S. or European professional societies for the management of generalized anxiety disorder.

CONCLUSIONS AND RECOMMENDATIONS

In patients who present with anxiety as a symptom, medical causes, such as hyperthyroidism, require consideration, as do common coexisting illnesses such as major depression, panic disorder, and substance abuse. For generalized anxiety alone or anxiety that is associated with depression, a reasonable first-line approach is to administer an SSRI or extended-release venlafaxine on the basis of the demonstrated efficacy of these drugs and their generally favorable side-effect profiles. To minimize side effects, particularly restlessness, one would start with a low dose and then increase it during the next three weeks or so until the target dose is reached (Table 2).

A four-to-five-week course of a benzodiazepine (e.g., clonazepam, given at a dose of 0.25 to 0.5 mg twice daily) may also be useful in reducing restlessness related to antidepressant therapy and in rapidly controlling anxiety. One would taper this dose during the next two to four weeks. Patients who prefer a nonpharmacologic approach should be referred for cognitive behavioral therapy and relaxation training. These therapies may also be useful in patients who take medication, although data are limited.

During the initiation of drug therapy, patients can be seen at intervals of two to four weeks, with the frequency decreased to every three to four months during maintenance therapy. If medication is effective, it should be continued for six months to a year and then tapered off, with monitoring for the recurrence of anxiety or depression, a finding that would require reinitiation of treatment. If a psychiatrist has not been consulted earlier, referral is advisable after two failed medication trials or when the patient has complex coexisting illnesses or suicidal ideation.

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