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In the Clinic®

Generalized Anxiety Disorder

Screening

Diagnosis

Treatment

Practice Improvement

Generalized anxiety disorder (GAD) is a common and disabling illness that is often underdiagnosed and undertreated. Patients with GAD are at increased risk for suicide as well as cardiovascular-related events and death. Most patients can be diagnosed and managed by primary care physicians. Symptoms include chronic, pervasive anxiety and worry accompanied by nonspecific physical and psychological symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbances). Effective treatments include psychotherapy (often cognitive behavioral therapy) and pharmacotherapy, such as selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors.

CME/MOC activity available at Annals.org.

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doi:10.7326/AITC201904020

CME Objective: To review current evidence for screening, diagnosis, treatment, and practice improvement of generalized anxiety disorder.

Funding Source: American College of Physicians.

Disclosures: Drs. DeMartini, Patel, and Fancher, ACP Contributing Authors, have nothing to disclose. The forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-3520.

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Anxiety can be an appropriate response to stressful situations but is considered a pathologic disorder when it is disabling and difficult to control. Generalized anxiety disorder (GAD) is the most common anxiety disorder seen in primary care, affecting approximately 4% to 7% of U.S. adults (1, 2). Patients with GAD have reduced global life satisfaction and lower health-related quality of life (3). GAD is characterized by at least 6 months of persistent and excessive anxiety; recurring worry about common events; and physical symptoms, such as muscle tension, insomnia, and fatigue combined with significant distress or impairment in personal, occupational, or other areas of function (4). More than one third of patients with GAD have decreased work productivity, with an average of 6.3 days of missed work per month (5). Patients with GAD have higher health care use and costs (more frequent emergency department visits, primary care visits, and referrals to specialty care) and higher overall prescription rates (6–9). These patients are at increased risk for suicide attempts (10), and those with co-occurring cardiovascular disease experience more cardiovascular events (myocardial infarction, heart failure, cerebrovascular accidents, transient ischemic attack, and death) (11, 12).

A large 10-year prospective cohort study of persons aged 45 years or older found that women with GAD had increased risk for cardiovascular death, independent of conventional cardiovascular disease risk factors and presence of metabolic syndrome as defined by the World Health Organization (hazard ratio, 1.94 [95% CI, 1.13 to 3.33]) (11).

The prospective Heart and Soul cohort study showed that patients with stable coronary heart disease and GAD had a 62% higher rate of cardiovascular events (hazard ratio, 1.62 [CI, 1.11 to 2.37]) than those with coronary heart disease only (12).

Screening

Who is at elevated risk for GAD?

GAD is twice as common in women as in men (13). Having low socioeconomic status; being widowed, separated, or divorced; or being middle-aged increases risk for GAD (14). Additional risk factors include comorbid psychiatric disorders (14, 15), history of substance abuse (16) or trauma (17), and family history of GAD (18). In older adults, new-onset GAD may develop in the context of chronic medical illnesses (19).

A meta-analysis of family and twin studies of common anxiety disorders showed a significant association of GAD between patients and their first-degree relatives, with an odds ratio of 6.1 (CI, 2.5 to 14.9) (18).

Are preventive measures useful for patients at elevated risk?

Although prevention or early intervention may reduce excess disability due to mental disorders, few studies have examined the effectiveness of preventive measures for GAD in adults. One study of patients with a recent stroke suggested that drug therapy and psychotherapy were beneficial for preventing GAD (20).

A randomized controlled study evaluated the effectiveness of prevention of GAD in 149 patients with recent stroke using escitalopram or problem-solving therapy. The study showed that patients who received placebo were 4.95 (CI, 1.54 to 15.93) times more likely to develop GAD than those given escitalopram and 4.00 (CI, 1.84 to 8.70) times more likely than those given problem-solving therapy (20).

Should clinicians screen patients for GAD if they are at increased risk? If so, how?

Current guidelines do not address recommendations on screening persons at increased risk for GAD, likely because of a

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PHQ–4: The 4-Item Patient Health Questionnaire for Anxiety and Depression

Over the last two weeks, how often have you been bothered by the following problems?

1. Feeling nervous, anxious, or on edge
   - 0: Not at all
   - 1: Several days
   - 2: More than half of the days
   - 3: Nearly every day
2. Not being able to stop or control worrying
   - 0: Not at all
   - 1: Several days
   - 2: More than half of the days
   - 3: Nearly every day
3. Feeling down, depressed, or hopeless
   - 0: Not at all
   - 1: Several days
   - 2: More than half of the days
   - 3: Nearly every day
4. Little interest or pleasure in doing things
   - 0: Not at all
   - 1: Several days
   - 2: More than half of the days
   - 3: Nearly every day

Total score is determined by adding together the scores of each of the 4 items.
Scores are rated as normal (0-2), mild (3-5), moderate (6-8), and severe (9-12).
Total score ≥3 for first 2 questions suggests anxiety.
Total score ≥3 for last 2 questions suggests depression.

paucity of high-quality studies showing a benefit to screening or early treatment. However, GAD is correctly diagnosed only one third of the time (21), and approximately 60% of persons who are diagnosed are not treated (22, 23). As seen in depression care, better detection may be the first step in addressing underdiagnosis and undertreatment and improving patient outcomes (24).

Screening tools to detect GAD vary in length, and many include screening for additional disorders. The single screening question, "Are you bothered by nerves?" has 100% sensitivity and 59% specificity among average-risk primary care patients (25). The 2-item Generalized Anxiety Disorder (GAD-2) screening tool asks how often patients have been bothered by "feeling nervous, anxious, or on edge" and "not being able to stop or control worrying" over the previous 2 weeks. Each question is scored as 0, 1, 2, or 3, for a total score of 0 to 6. A score of 3 or more has sensitivity of 86% and specificity of 83% for detecting GAD (2).

The 4-item Patient Health Questionnaire (PHQ-4) (see the **Box**) provides a brief and accurate screen for both major depressive disorder and GAD by combining the GAD-2 tool with the PHQ-2 (which has sensitivity of 83% and specificity of 90% for major depressive disorder) (26).

Kroenke and colleagues found no significant difference between the GAD-7 and the GAD-2 in screening of primary care patients (2).

Patients with a positive result on any screening tool should be

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Diagnostic Criteria for Generalized Anxiety Disorder

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 individual finds it difficult to control the worry.

The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

- Restless or feeling keyed up or on edge.
- Being easily fatigued.
- Difficulty concentrating or mind going blank.
- Irritability.
- Muscle tension.
- Sleep disturbances (difficulty falling or staying asleep, or restless, unsatisfying sleep).

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 attributable to the physiologic effects of a substance (e.g., drug of abuse, medication) or another medical condition (e.g., hyperthyroidism).

The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical problems in somatic symptom disorder, body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Patients must meet all 6 criteria for a diagnosis of generalized anxiety disorder.

further evaluated to assess whether they meet the diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (see the **Box:** Diagnostic Criteria for Generalized Anxiety Disorder) (4).

Screening... Clinicians should consider screening for GAD among adults who are at increased risk. Multiple screening tools have similar sensitivity and specificity, so a busy clinician can use a tool with just a few questions.

CLINICAL BOTTOM LINE

Diagnosis

What symptoms should prompt clinicians to consider a diagnosis of GAD?

Symptoms of excessive anxiety and worry about everyday events and problems should prompt clinicians to consider GAD. To meet the DSM-5 criteria for GAD (**Box**: Diagnostic Criteria for Generalized Anxiety Disorder), the excessive anxiety and worry (apprehensive expectation) must be difficult to control; must result in distress or marked trouble in performing day-to-day tasks; and must be associated with 3 or more of the following symptoms occurring on more days than not for at least 6 months: restlessness, being easily fatigued, difficulty

concentrating, irritability, muscle tension, or sleep disturbance (4). The remaining diagnostic criteria relate to ruling out other mental and physical conditions that can mimic GAD. Clinicians must ensure that the patient's symptoms are not attributable to physiologic effects of medications, drug abuse, or other medical conditions (such as hyperthyroidism) and are not better explained by a different mental disorder, such as posttraumatic stress disorder, obsessive-compulsive disorder, or delusional beliefs in schizophrenia or delusional disorder. In contrast to GAD, these other anxiety disorders are often associated with a specific primary stimulus. Posttraumatic stress disorder is associated with threatened death, serious injury, or sexual violence; obsessive-compulsive disorder is associated with intrusive and upsetting thoughts, images, or urges (obsessions) and rituals (compulsions) to reduce distress about them; and anorexia nervosa and body dysmorphic disorder are associated with a fixation on idealized physical appearance.

What physical examination findings indicate possible GAD?

A patient with GAD can seem restless, irritable, fatigued, or tense. In primary care settings, patients with GAD may also have medically unexplained symptoms, such as chest pain and rapid heart rate (24). A thorough physical examination is necessary and may uncover an underlying or co-occurring medical condition that requires further evaluation (1).

What laboratory tests should clinicians use?

No laboratory testing is necessary to diagnose GAD. However, clinicians should consider directed laboratory testing to exclude medical conditions suggested by the presenting symptoms and physical signs found during the evaluation (27). Among the most useful tests in patients presenting with symptoms of anxiety are thyroid function tests to exclude thyroid disease, hemoglobin measurement to exclude anemia, and urine drug screening if substance use is a potential concern. Other routine laboratory tests have a low yield. Catecholamine measurement to check for pheochromocytoma should be limited primarily to persons with a family history of endocrine disorders or those with episodic hypertension, headaches, and palpitations.

What other diagnoses should clinicians consider?

When evaluating patients for GAD, clinicians should consider medical conditions (for example, cardiac, pulmonary, or endocrine illnesses), mood and other anxiety disorders, adverse effects of prescribed or over-the-counter medications and supplements, and substance misuse and withdrawal. Several physical and mental disorders can mimic or co-occur with GAD (**Table 1**).

Of note, more than half of patients with GAD have a comorbid mental illness, such as depression, panic disorder, or social anxiety disorder (13). Major depressive disorder is a common coexisting mental illness and may be difficult to distinguish from GAD because of overlapping symptoms (for example, irritable mood, fatigue, and insomnia). Anhedonia and feelings of hopelessness are common symptoms of major depressive disorder but not GAD, which is more often associated with feelings of helplessness. Other anxiety disorders can be distinguished from GAD by their defining characteristics. Patients with panic disorder

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Table 1. **Differential Diagnosis for Generalized Anxiety Disorder**

Disease	*Notes*
Cardiopulmonary disorders, such as asthma, chronic obstructive pulmonary disease, or congestive heart failure	These disorders can co-occur with generalized anxiety disorder or mimic anxiety symptoms. Medications used to treat these disorders, such as β-agonists, may also cause symptoms mimicking generalized anxiety disorder.
Endocrine disease, including thyroid disorders, diabetes, and hypoglycemia	Many endocrine disorders (most commonly hyperthyroidism, hypoglycemia, or hypothyroidism) can mimic anxiety symptoms. Consider thyroid function tests and blood glucose testing. Consider catecholamine level testing for evaluation of pheochromocytoma in patients with a family history of endocrine neoplasms or those with episodic headaches, hypertension, and palpitations.
Mood disorders, including major depressive disorder and bipolar disorder	Given overlapping symptoms, depressive disorders should be considered in the differential diagnosis. Generalized anxiety disorder and mood disorders frequently co-occur; symptoms of mood disorders should be treated first. As the mood disorder is treated, symptoms of generalized anxiety disorder may become more apparent.
Other anxiety disorders, including simple or social phobia, panic disorder, obsessive-compulsive disorder, acute stress disorder, and posttraumatic stress disorder	In generalized anxiety disorder, patients worry about several different topics, in contrast to other anxiety disorders, where there is often a specific and primary generator of anxiety symptoms. Generalized anxiety disorder can co-occur in the presence of any other anxiety disorder.
Prescribed and over-the-counter medications	Effects of corticosteroids, sympathomimetics, and herbal medications (such as ginseng) may mimic symptoms of generalized anxiety disorder.
Misuse of such substances as alcohol, benzodiazepines, caffeine, nicotine, amphetamine, cocaine, and other stimulants	Stimulant (nicotine, caffeine, amphetamines, cocaine, and various "party pills") intoxication can cause anxiety and mimic generalized anxiety disorder. Anxiety is also a symptom of alcohol and benzodiazepine withdrawal. Consider ordering a drug screen and taking a detailed history if substance use is suspected.

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experience recurrent, unexpected, transient surges of intense fear with physical symptoms (fast heart rate, chest pain, dyspnea, dizziness, or paresthesia) and excessive anxiety over these episodes. Patients with social anxiety disorder have anxiety about being scrutinized and fear of being embarrassed when interacting with other people. A person who is preoccupied with having or developing a serious, undiagnosed medical condition may have a health or illness anxiety disorder.

Effects of prescribed and over-the-counter medications, such as corticosteroids, sympathomimetics (for example, phenylephrine), and herbal supplements (for example, ginseng) can mimic symptoms of GAD. Approximately 8% to 10% of patients with GAD use alcohol and benzodiazepines to alleviate anxiety symptoms, so clinicians should be vigilant in assessing for substance misuse and withdrawal (28). If symptoms of anxiety persist after appropriate treatment of physical and other mental disorders, clinicians should consider screening for GAD.

Epidemiologic data indicate that 69% to 95% of patients with GAD have a co-occurring psychiatric disorder. Between 45% and 70% have a comorbid mood disorder (mainly depression), and 38% to 56% have another anxiety disorder, such as panic disorder, social anxiety disorder, or posttraumatic stress disorder (13).

When should clinicians consider consulting a psychologist, psychiatrist, or other specialist?

Most patients with GAD can be diagnosed by a primary care physician. However, in cases of diagnostic uncertainty or multiple comorbid mental health conditions, clinicians should consider obtaining a second opinion from

a psychologist, psychiatrist, or other mental health specialist.

What cross-cultural approaches should clinicians consider?

In our increasingly multicultural population, clinicians must be aware that contextual information related to a patient's background (language, culture, race, ethnicity, religion, or geographic origin) may influence expressions of distress, help-seeking behaviors, presentation of symptoms, treatment expectations, and acceptance of diagnosis and treatment recommendations (29). Different cultures and communities may express or interpret symptoms in ways that differ from the medical conceptualization of mental illness based on the DSM-5 criteria. For example, somatization is common across all cultures, but persons from non-Western cultures may be more likely to report somatic symptoms, such as dizziness or indigestion, which are not included in the DSM-5 (30). Also, the choice of words in assessment of anxiety symptoms is important. A study conducted in Peru found low rates of use of the Spanish equivalent of "uncontrollable," but the same respondents frequently indicated difficulty in controlling worrying ("Once I start worrying, I cannot stop") (31). In a study conducted in Hong Kong, the prevalence of GAD increased by more than 4-fold when investigators removed the "excessive" criteria from the DSM-5 definition to better align with the World Health Organization's classification of GAD (32). To provide patient-centered care to a diverse community, clinicians can use the LEARN model of cross-cultural health care communication (**Listen** with empathy and understanding to your patient's perception of the problem, **Explain** your perceptions of the problem, **Acknowledge** and discuss the differences and similarities and recognize cultural influences, **Recommend** a treatment plan that respects and fits within the patient's parameters, **Negotiate** an agreement with the patient on a course of action) (33).

The DSM-5's Outline for Cultural Formulation provides a detailed guide of questions for clinicians to use to understand their patient's cultural identity and conceptualization of illness, cultural features of vulnerability and resistance, and cultural factors in the relationship between the patient and the clinician (4). The Office of Minority Health sponsors a free online continuing medical education module to help providers deliver culturally competent care (34).

Diagnosis... A thorough history is the foundation of diagnosing GAD. To better serve a multicultural population, clinicians can use the LEARN mnemonic to improve communication with patients. Laboratory testing in most patients with GAD can be deferred unless underlying medical disorders are suspected. Comorbid mental illness and substance misuse are common among patients with GAD and should be assessed in each patient. Clinicians should consider consulting a mental health specialist if the diagnosis of GAD is uncertain.

CLINICAL BOTTOM LINE

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Treatment

What nondrug therapies should clinicians recommend for GAD?

Although various psychotherapeutic approaches delivered on an individual or group basis can be used to treat GAD (with or without adjunctive medications), those in the family of cognitive behavioral therapy (CBT) have the largest body of evidence (**Table 2**) (35). The basic goal of CBT is to identify and change unhelpful thoughts and behaviors to improve emotions and quality of life. For example, a patient with GAD might worry about the well-being of a loved one and therefore engage in a behavior to avoid that anxiety (such as calling to check on the loved one), which results in a temporary reduction but long-term maintenance of anxiety. Furthermore, the process of worrying may reduce physiologic arousal and is therefore reinforcing and serves as an avoidance strategy (36). Some CBT techniques, especially exposure therapy, may temporarily increase distress but eventually lead to reduction in chronic anxiety. Types of exposure therapy include imaginal (vividly imagining the feared object, situation, or activity), in vivo (directly facing a feared object, situation, or activity in real life), and interoceptive (deliberately bringing on physical sensations that are harmless but feared). Other commonly used techniques in CBT include education; goal setting; self-monitoring; cognitive restructuring; relaxation training, including biofeedback; and problem solving. A typical CBT course for GAD lasts approximately 12 sessions and includes substantial homework for patients to practice between sessions. Unfortunately, access to CBT practitioners is limited (4, 37, 38). One approach to increase access is through Internet-based CBT for anxiety (39), which requires minimal therapist involvement and has been shown to be effective (40, 41); however, this approach is not yet widely available outside the research setting. CBT may also be completely self-directed through books or smartphone apps. Although the latter are a cost-effective way of delivering treatment to the population (42), there are concerns about security and privacy, as well as adverse effects related to overuse of electronic devices (43). Clinicians also need to be aware that most self-help books and apps that are available for download on smartphones have not been rigorously tested (44).

A meta-analysis of 92 studies (8403 participants) found that a wide range of self-help CBT interventions (including books, audiotapes, videotapes, and Internet programs) are better than wait-list controls, with a moderate to large effect size of 0.67 (CI, 0.55 to 0.80), but are likely inferior to face-to-face CBT (effect size, −0.23 [CI, −0.36 to −0.09]) (38).

A recent meta-analysis of 9 randomized controlled trials (1837 participants) found that psychological interventions for anxiety disorders delivered by smartphone had a small to moderate effect size (0.325 [CI, 0.17 to 0.48]) compared with controls (45).

Other types of psychotherapies (**Table 2**) should be considered if CBT is unavailable or ineffective. Supportive psychotherapy and psychodynamic therapy are commonly available to patients with anxiety, but the few comparison studies that exist suggest they may have inferior treatment outcomes to CBT for GAD (46–49). Mindfulness meditation and acceptance and commitment therapy share similarities with CBT and have been shown to be effective in treating GAD, but few studies have compared these

treatments with CBT (50–52). Some patients may use herbal remedies to treat anxiety, and clinicians should inquire about their use and counsel patients on any known drug interactions or toxicities. For example, Kava, a beverage made from a root originating in the Pacific islands where it has long been used for traditional medicine purposes, has been shown to significantly reduce anxiety in the short term, but there are concerns about its safety, including (very rarely) liver toxicity (53). Healthy lifestyle choices, including avoiding recreational drugs and limiting alcohol consumption, practicing good sleep hygiene, and exercising regularly, should be emphasized as important elements of mental health.

A recent meta-analysis showed that exercise has a moderate effect size (−0.41 [CI, −0.70 to −0.12]) compared with wait-list controls (54). High-intensity exercise was found to be better than low-intensity exercise, with an effect size of −0.38 (CI, −0.68 to −0.08), although it seemed to have higher dropout rates.

How should clinicians choose drug therapy and the dose?

For most adults with GAD, clinicians should offer drug therapy if nondrug therapies are ineffective or the patient is not interested in them (**Table 3**). Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are recommended as first-line drug therapies because of their tolerability and efficacy compared with other drug therapies (55). They have fewer long-term risks than other drugs commonly used to treat anxiety and have the added benefit of treating major depression, which is often co-occurring (56). SSRIs that are approved by the U.S. Food and Drug Administration for GAD include paroxetine, sertraline, and escitalopram, and approved SNRIs include venlafaxine extended-release and duloxetine. Other SSRIs and SNRIs have not been studied as rigorously, although off-label use may be considered given their similar mechanism of action and benefit in related disorders. Low doses should be considered initially (for example, sertraline, 25 mg/d, or venlafaxine extended-release, 37.5 mg/d) because patients with anxiety may be particularly sensitive to

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Table 2. **Psychotherapies for Patients With Generalized Anxiety Disorder**

Type of Therapy	*Notes*
Cognitive behavioral therapy	This therapy is traditionally delivered in 12 sessions and focuses on examining and changing unhelpful thoughts and behaviors that perpetuate anxiety. Elements of cognitive behavioral therapy may also be learned with minimal therapist involvement or through self-help tools (using books, audio/video, the Internet, and smartphone apps), although many have not been rigorously tested. Techniques include education, exposure therapy, relaxation training and biofeedback, and problem-solving techniques.
Supportive psychotherapy	A commonly practiced and nondirective form of therapy that focuses on supporting the patient's self-esteem. In a warm and nonjudgmental environment, the therapist carefully listens to the patient and provides reassurance and encouragement.
Psychodynamic therapy	An insight-oriented form of therapy that aims to resolve unconscious conflicts that are believed to result from early-life relationships. Techniques include clarifications, interpretations, and confrontations.
Mindfulness	A type of meditation in which patients learn to increase awareness of the present. Patients are encouraged to focus on bodily sensations, emotions, and thoughts in a nonjudgmental manner.
Acceptance and commitment therapy	This therapy shares similarities with mindfulness and cognitive behavioral therapy. Patients learn to focus on the present and accept thoughts or practice strategies to distance themselves from internal thoughts and sensations, a technique called cognitive defusion.

Table 3. **Drug Treatment for Generalized Anxiety Disorder**

Class of Agent	*Specific Agent, Therapeutic Dose*	*Benefits*	*Adverse Effects and Notes*
First-line medications: selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs)		As a class: effective, well tolerated	As a class: nausea, diarrhea, decreased appetite, restlessness, insomnia, somnolence, impaired sexual function, and hyponatremia
SSRI	Escitalopram, 10–20 mg/d	Few drug interactions	QTc prolongation 10 mg/d is maximum dose recommended for elderly adults and those with hepatic impairment
SSRI	Paroxetine, 20–60 mg/d	Long clinical experience	More weight gain and sedation; discontinuation syndrome not uncommon Increased drug interactions, including strong CYP2D6 inhibition
SSRI	Sertraline, 50–200 mg/d	Long clinical experience, fewer drug interactions	Higher incidence of gastrointestinal distress
SNRI	Duloxetine, 60–120 mg/d	Also effective for neuropathic and chronic musculoskeletal pain	Higher incidence of gastrointestinal distress
SNRI	Venlafaxine extended-release, 75–225 mg/d	Also effective for migraine, neuropathic pain, vasomotor symptoms from menopause	May increase blood pressure
Second-line medications			
Azapirones	Buspirone, 15–30 mg/d	As a class: lack abuse potential and are not addictive; can be used for augmentation	Dizziness, drowsiness
Benzodiazepines	Alprazolam, 0.5–2 mg/d; diazepam, 2–10 mg/d; chlordiazepoxide, 15–40 mg/d	As a class: very effective in the short term; faster onset of action than antidepressants	As a class: falls, memory impairment, risk for dependence
Anticonvulsant	Pregabalin, 300–600 mg/d	Well tolerated; early effect	Sedation, dizziness, peripheral edema Use with caution in patients with renal impairment
Third-line medications			Clinicians should consider consulting with a mental health specialist if they are unfamiliar with these therapies
Atypical antipsychotics	Quetiapine, 50–300 mg/d; risperidone, 0.5–1.5 mg/d	Also effective for mood and psychotic disorders	As a class: sedation, extrapyramidal symptoms, tardive dyskinesia, weight gain, and metabolic adverse effects
Antihistamine	Hydroxyzine, 50–100 mg 4 times daily	Potentially useful for treatment of insomnia associated with generalized anxiety disorder	Sedation, dry mouth, confusion, and urine retention
Tricyclic antidepressants	Imipramine, 50–200 mg/d	Long history of efficacy in depression and anxiety	Lethal in overdose Adverse effects include arrhythmias, orthostatic hypotension, blurred vision, and constipation

the adverse effects associated with initiation, including gastrointestinal distress, dizziness, and restlessness. These effects often improve after the first week or two. If the medication is well tolerated and/or there is a partial response (see the next section), the clinician should consider titrating to a therapeutic dose, which may be higher than what is typically needed for major depression. If there is no response after 8 weeks of a therapeutic dose of an SSRI or an SNRI, clinicians should consider switching to another agent in these classes before trying another medication (1).

Second-line agents include azapirones, such as buspirone, benzodiazepines, and pregabalin. Buspirone may be equivalent to benzodiazepines in treatment of GAD (56, 57). However, sedation and dizziness are common adverse effects of these drugs, and they can also take weeks to achieve their effect. Benzodiazepines can effectively treat anxiety symptoms in the short term (2 to 4 weeks) if, for example, a patient is waiting for the anxiolytic properties of an SSRI or an SNRI to take effect (19). However, studies on the long-term efficacy of benzodiazepines are lacking, and they are associated with a significant risk for sedation, motor and cognitive impairment, and dependence. Therefore, long-term use of anxiolytics should be discouraged (1, 56). Benzodiazepines should be avoided in patients who have a substance use disorder or are

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69. Martin P, Tannenbaum C. A realist evaluation of patients' decisions to deprescribe in the EMPOWER trial. BMJ Open. 2017;7:e015959. [PMID: 28473524]

using other high-risk sedatives, such as opiates, especially without a plan to taper or consultation with a psychiatrist. Pregabalin, which was developed as an antiepileptic, has been shown to be efficacious for GAD and well tolerated in several randomized controlled trials, with an earlier response than SSRIs and SNRIs (58). Although pregabalin may not be as habit forming as benzodiazepines, caution is still advised in patients with a history of substance abuse, and there is increased risk for adverse effects, including sedation, in elderly persons and those with renal impairment.

If first- or second-line agents are ineffective or poorly tolerated, alternative options include atypical antipsychotics, such as quetiapine or risperidone (59, 60); hydroxyzine (61); and tricyclic antidepressants, such as imipramine (56). Clinicians should consider consulting a mental health specialist before prescribing these third-line agents given their significant adverse effects.

How should clinicians monitor patients?

Patients with GAD should be monitored in person or by telephone every 2 to 4 weeks until they are stable and then every 3 to 4 months during maintenance therapy. Structured instruments, including the GAD-7 (**Table 4**), may help clinicians monitor symptom severity and response (62). Each response in the GAD-7 is assigned a value of 0, 1, 2, or 3; summary scores of 5, 10, and 15 are cutoffs for mild, moderate, and severe anxiety, respectively. There are no formal recommendations for treatment discontinuation or augmentation based on GAD-7 scores, but a reduction of 5 or more points is typically considered a meaningful partial response. Downloadable versions of this instrument are available in more than 50 languages (63). The new DSM-5 includes additional monitoring instruments, including one that monitors symptom severity in adults with GAD (64). However, these instruments have not been evaluated as rigorously as the GAD-7 and may be more cumbersome to use in a busy primary care practice. In addition to symptom assessment, clinicians should routinely ask about medication adherence, treatment adverse effects, and suicide risk.

Anxiety relapses are common, especially in response to interpersonal conflict, social pressure, or other negative emotional states. CBT strategies include learning how to maintain cognitive and behavioral changes and

Table 4. **Generalized Anxiety Disorder 7-Item Scale***

Over the Last 2 Weeks, How Often Have You Been Bothered by the Following Problems?	*Not at All*	*Several Days*	*Over Half the Days*	*Nearly Every Day*
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

**Total score is determined by summing the scores for each item. A score of 5 to 9 indicates mild anxiety, 10 to 14 indicates moderate anxiety, and 15 to 21 indicates severe anxiety.*

70. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. JAMA Intern Med. 2014;174:890-8. [PMID: 24733354]
71. National Collaborating Centre for Mental Health. NICE Quality Standard QS53: Anxiety Disorders. London: National Institute for Health and Care Excellence; 2014. Accessed at www.nice.org.uk/guidance/qs53 on 12 November 2018.
72. National Collaborating Centre for Mental Health. NICE Clinical Guideline 113: Generalised Anxiety Disorder and Panic Disorder in Adults: Management. London: National Institute for Health and Care Excellence; 2011. Accessed at http://guidance.nice.org.uk/CG113 on 25 November 2018.
73. Canadian Psychiatric Association. Choosing Wisely Canada. Accessed at https://choosingwisely-canada.org/wp-content/uploads/2017/02/Psychiatry.pdf on 12 November 2018.

how to anticipate and cope with relapse. During a relapse, patients may benefit from additional CBT to reinforce their previous knowledge or modify practices for their current situation. Pharmacotherapy should be continued for 6 to 12 months after symptom response is achieved (64). After discontinuation of medication use, 20% to 40% of patients relapse within 6 to 12 months (65, 66). Some patients with severe chronic anxiety for many years may require long-term medication (>1 year) (65).

A trial of continuation of treatment among 429 patients with GAD who had responded previously to duloxetine found that only 13.7% who continued treatment relapsed over the 26-week continuation phase compared with 41.8% of those receiving placebo during the same period (66).

When should patients be hospitalized?

Although most patients with GAD can be treated as outpatients, those who are suicidal should be hospitalized. Suicidal ideation is not uncommon in patients with GAD with or without co-occurring depression. Clinicians should assess risk for suicide in all patients with GAD at each follow-up encounter (67). Many of the screening and monitoring instruments used for anxiety do not include a question about suicidality, so clinicians should consider asking the following question from the PHQ-9: "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" (63).

In a large meta-analysis of suicidal behaviors that compared persons with and without anxiety disorders, the subgroup of patients with GAD were at particularly high risk for suicide attempts, with an odds ratio of 2.7 (CI, 1.92 to 3.79) (10).

Hospitalization might also be required for intractable symptoms, for grave disability, or to address co-occurring illness. GAD can complicate treatment of co-occurring disorders and adversely affects prognosis.

When should clinicians consider consulting a psychologist, psychiatrist, or other specialist?

Consultation with a mental health professional should be considered if the diagnosis is uncertain or the patient does not respond to a full course of CBT or 1 to 2 trials of a serotonin reuptake inhibitor with an adequate dose and duration. Consultation is also warranted if patients are unable to tolerate drug therapy; express suicidal thoughts; or have comorbid substance, mood, or other anxiety disorders or if the clinician is considering prescribing long-term benzodiazepines or third-line medications.

Treatment... Primary care physicians play an important role in managing anxiety disorders. CBT is the treatment of choice for GAD in most adults. If CBT is unavailable or ineffective or if the patient is not interested in nondrug therapy, SSRIs and SNRIs are the first-line medication options. Clinicians should assess risk for suicide in all patients with GAD and refer more complex patients to mental health specialists.

CLINICAL BOTTOM LINE

How should clinicians educate patients about managing their anxiety symptoms?

Clinicians should reassure patients that occasional worry or anxiety in response to threats to one's life or well-being is common and normal. They should advise patients to seek mental health care if their worries are numerous and are affecting their ability to focus on daily activities, and they should inform patients that such treatments as lifestyle adjustments, psychotherapy, and medication are beneficial.

Clinicians should emphasize that treatments may take weeks or months to become fully effective and that several treatments may sometimes be needed to find the best one for an individual patient. They should consider referring patients to the National Alliance on Mental Illness, a national grassroots advocacy group and a comprehensive resource for patients and their families to learn more about anxiety and to find online or local support groups.

Given safety concerns related to long-term benzodiazepine use, it is important for clinicians to reassess patients with long-term use of these medications. If the clinician deems benzodiazepines to be ineffective or unsafe or if the patient has not completed psychotherapy or first-line pharmacotherapy, the clinician should consider educating the patient about discontinuing these drugs.

Clinician guidelines and algorithms for discontinuation, educational pamphlets from the EMPOWER (Eliminating Medications Through Patient Ownership of End Results) trial, and information about stopping use of other common medications that are potentially harmful or no longer needed are available online (68). The motivation to discontinue use has been found to be associated with improved knowledge, increased concern about the drugs, and increased self-efficacy, whereas failure to discontinue was associated with lack of support from a health care provider, focus on short-term quality of life, intolerance of withdrawal symptoms, and perceived poor health (69).

The EMPOWER trial randomly assigned 303 patients who were aged 65 years or older and had long-term prescriptions for benzodiazepines and other hypnotics to receive either an educational pamphlet from their pharmacy on the risks associated with these agents and a suggested slow tapering protocol, or usual care (70). Twenty-seven percent of patients in the intervention group versus 5% in the control group completely discontinued benzodiazepine use at 6 months (risk difference, 23% [CI, 14% to 32%]). In the intervention group, 62% initiated conversations with their pharmacist or physician about stopping use of benzodiazepines.

Are there measures that stakeholders use to evaluate quality of care for patients with GAD?

Although there are no quality-of-care measures specifically for GAD, the U.K. National Institute for Health and Care Excellence (NICE) published a list of quality statements for anxiety disorders in 2014 (71). These standards specify that persons with a suspected anxiety disorder should receive an assessment that identifies whether they have a specific anxiety disorder, the severity of symptoms, and associated functional impairment; those with an anxiety disorder should be offered evidenced-based psychological interventions and should not be prescribed benzodiazepines or antipsychotics unless they are specifically indicated; and those being treated for an

anxiety disorder should have their treatment response recorded at each session.

What do professional organizations recommend with regard to care of patients with GAD?

There are currently no formal practice guidelines from U.S. professional societies for management of GAD. The NICE published clinical guidelines for GAD and panic disorder in 2011 that describe a stepped-care model for GAD management (72). Step 1 involves patient education and active monitoring as first-line treatment. Step 2 involves low-intensity psychological interventions for patients who do not improve with step 1. Step 3 involves CBT or drug treatment for patients who do not respond to step 2 or who have marked functional impairment. Step 4 (the final step) involves mental health specialists, complex drug and/or psychological treatment regimens, and hospitalization for treatment-refractory patients or persons at risk for self-harm or self-neglect. As part of the Choosing Wisely Canada campaign, which was updated in 2017, the Canadian Psychiatric Association acknowledged that benzodiazepines can be helpful for short-term treatment of anxiety, but serious adverse effects, including cognitive and motor impairment and problems with abuse and dependence, need to be considered (73). The Canadian Psychiatric Association recommends against routine continuation of benzodiazepines started during hospitalization and recommends making a plan to taper on the prescription and discharge summary before the patient is discharged.

In the Clinic
Tool Kit

Generalized Anxiety Disorder

Patient Information

https://medlineplus.gov/anxiety.html
https://medlineplus.gov/ency/article/000917.htm
https://medlineplus.gov/spanish/ency/article/000917.htm
Resources related to anxiety from MedlinePlus of the National Institutes of Health, including patient handouts in English and Spanish.

www.nimh.nih.gov/health/publications/generalized-anxiety-disorder-gad/index.shtml
www.nimh.nih.gov/health/publications/espanol/trastorno-de-ansiedad-generalizada-cuando-no-se-pueden-controlar-las-preocupaciones-new/index.shtml
Patient handouts on generalized anxiety disorder in English and Spanish from the National Institute of Mental Health.

www.nimh.nih.gov/health/publications/generalized-anxiety-disorder-gad/generalized-anxiety-disorder_124169.pdf
Generalized Anxiety Disorder: When Worry Gets Out of Control patient handout from the National Institute of Mental Health.

www.psychiatry.org/patients-families/anxiety-disorders
Help with anxiety disorders from the American Psychiatric Association.

www.aafp.org/afp/2015/0501/p617-s1.html
Help for Anxiety and Panic Disorders patient handout from the Anxiety and Depression Association of America, released in 2015.

Clinical Guidelines and Other Information for Health Professionals

www.aafp.org/afp/2015/0501/p617.html
Diagnosis and management of generalized anxiety disorder and panic disorder in adults from the American Academy of Family Physicians, released in 2015.

https://adaa.org/resources-professionals/practice-guidelines-gad
Clinical practice review for generalized anxiety disorder from the Anxiety and Depression Association of America, released in 2015.

WHAT YOU SHOULD KNOW ABOUT GENERALIZED ANXIETY DISORDER

What Is Generalized Anxiety Disorder?

Feeling worried or anxious is a normal response to stressful situations. However, constant feelings of worry that disrupt your daily life may be a sign of a condition called generalized anxiety disorder (GAD).

What Are the Symptoms?

GAD is a common, disabling condition. People with GAD have trouble controlling their feelings of worry and have other symptoms that interfere with their daily life for at least 6 months, including:

- Restlessness or feeling "on edge"
- Tiring easily
- Muscle tension
- Irritability
- Trouble concentrating
- Insomnia (trouble falling or staying asleep)

Am I at Risk?

GAD can happen to anyone but is more common in women. Anxiety disorders run in families, so having a family history of GAD can increase your risk. If you have another psychiatric disorder or a history of substance abuse or trauma, you may also be at increased risk for GAD.

How Is It Diagnosed?

- Your health care provider will ask questions about your symptoms and conduct an examination.
- He or she will rule out other medical conditions or mood disorders that could be causing your symptoms.
- Laboratory tests may be done to rule out other conditions that cause similar symptoms.

How Is It Treated?

Your health care provider will probably recommend you try nondrug treatments for GAD first, such as:

- A type of talk therapy called cognitive behavioral therapy can help to identify and change unhelpful thoughts and behaviors to improve your quality of life.
- Relaxation techniques, like mindfulness meditation.
- Lifestyle changes, like avoiding drugs, limiting alcohol intake, and exercising regularly.

Drug treatments for GAD are available if nondrug treatments do not work.

- Several antidepressants work well for treatment of GAD.
- You should use benzodiazepines only if you do not respond to other medicine and do not have a history of substance use disorder. They are habit forming and do not work in the long term.

You may need several weeks of treatment before you notice an improvement. Once your treatment starts to work, you should continue it for at least 6 to 12 months to avoid relapse.

Questions for My Doctor

- Are my feelings of worry excessive?
- How can I manage my symptoms?
- Do I need to see a therapist?
- Do I need to take medicine?
- What medicine is best for me?
- What are the side effects of the medicine?
- Are there support groups for me or my family?

For More Information

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Anxiety and Depression Association of America
https://adaa.org/understanding-anxiety/generalized-anxiety-disorder-gad

National Institute of Mental Health
www.nimh.nih.gov/health/publications/generalized-anxiety-disorder-gad/index.shtml

Patient Information