Generalized anxiety disorder (GAD) is a common condition, with a lifetime prevalence of approximately 5% in the United States adult population according to the Epidemiological Catchment Area (ECA) study [1]. In comparison, Kendler et al [2] reported a lifetime prevalence of 3.6%. The National Comorbidity Survey reported a lifetime prevalence of 5.1% [3]. An international (World Health Organization) study indicated that GAD was the second most frequent psychiatric disorder after depression in the primary care setting, with approximately 8% of primary care patients meeting diagnostic criteria [4,5]. Risk for GAD is slightly higher among women.

GAD has a relatively early onset and is typically a chronic illness [6]. The ECA survey reported that approximately one third of individuals with GAD had an age of onset in the teens or early twenties [1]. Frequently, however, the first contact with a health professional is not until young adulthood or later. The course of illness of GAD tends to be chronic and recurrent. The ECA survey found that almost 50% of individuals who had ever experienced GAD continued to be ill at the time of interview, and the mean duration of illness was reported to be 6 to 10 years [1].

Significant distress and disability are associated with GAD. Excellent information is currently available on the disability and quality of life effects of GAD from the ECA community survey [1] and from a multisite survey of psychiatric outpatients [7]. The overall picture for GAD is one of significant psychosocial impairment. Of those patients who were working, 38% had missed at least 1 week of work in the past year due to their anxiety [7]. Greenberg et al [8] estimated the cost of all anxiety disorders to be approximately $42.3 billion in 1990 in the United States. Rice and Miller [9] reported similar economic costs.

CASE STUDY
Initial Presentation

A 32-year-old woman presents to her family physician with a chief complaint of palpitations experienced intermittently since childhood.

History

She reports that in addition to her palpitations, she feels worried a lot and has trouble controlling the worry. She adds that she feels tense and on edge, has been irritable with her friends, and is having difficulty concentrating at work. She reports that she has been a chronic worrier since her early teenage years but has never sought treatment for her symptoms. Her symptoms have seemed more severe during the past 6 months, leading her to consult her physician.

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The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms being present for more days than not during a 6-month period)

1. Restlessness, 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

The focus of the worry is not confined to features of an Axis I disorder (eg, mood disorder, schizophrenia, psychotic disorder) during exacerbations of an Axis I disorder (eg, mood disorder, schizophrenia, psychotic disorder) and does not occur exclusively in the context of a general medical condition (eg, hyperthyroidism) and does not occur exclusively during exacerbations of an Axis I disorder (eg, mood disorder, psychotic disorder)

The worry and physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

The symptoms are not due to a substance or a medical condition (eg, hyperthyroidism) and does not occur exclusively during exacerbations of an Axis I disorder (eg, mood disorder, psychotic disorder)

The patient has no significant medical illness. She had a tumor when the patient was age 12.

She describes a happy childhood until her sister became ill. Her parents divorced 10 years ago. She excelled in school and had several scholarships. She completed a PhD in folklore at a prominent university and now works for a medical publishing firm as an editor. She lives with her husband in their own home. Her husband is a successful writer whom she met at university. They have been married for 6 years; it is a happy marriage. Their children are healthy.

**Physical Examination**

The patient is a well-developed woman who appears her stated age. She is casually and neatly dressed, adequately groomed, and thin. No psychomotor retardation or agitation is noted. Speech is within normal limits in tone, volume, and rate. Thought content is without obsessions, delusions, or hallucinations. There is no suicidal ideation. Cognitive function is unimpaired; Mini-Mental State Examination score is 29.

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**Does this patient meet diagnostic criteria for GAD?**

**Which disorders should be included in the differential diagnosis of GAD?**

This patient meets the diagnostic criteria for GAD, which are listed in the Table. Asking patients if they spend a lot of time worrying about various things (eg, job, hobbies, friends) and if the worries seem out of control or interfering with life may help identify those who have the disorder. Additional clinical history should be obtained to confirm the diagnosis. It is worth noting that because anxiety symptoms of GAD can be so troubling, some patients may present with less than 6 months’ duration of symptoms. In patients with less than 6 months of symptoms who otherwise meet criteria for GAD, the accepted diagnosis is adjustment disorder with anxious mood.

Several other anxiety disorders might be considered in the differential diagnosis of GAD, including social phobia and panic disorder. In social phobia, anxiety symptoms are attached to specific situations in which the person encounters unknown individuals or is under the scrutiny of others. Commonly, these situations include crowds of people or occasions when the affected individual must perform in some manner. The patient with social phobia will often express the fear that an embarrassing event will occur. Social situations are avoided frequently, and the fear is recognized as unreasonable. In contrast, the apprehension and worry of GAD is global and unrestricted to particular situations. The GAD patient shares with the panic disorder patient a chronic apprehension or worry, but will not endorse the very sudden onset (“out of the blue”) of panic attacks without provocation. In addition, the panic disorder patient will

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**Table. DSM-IV 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 different events or activities (eg, work, school performance and leisure activity)

B. The person finds it difficult to control the worry

C. The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms being present for more days than not during a 6-month period)

1. Restlessness, 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

D. The focus of the worry is not confined to features of an Axis I disorder: the worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), gaining weight (as in anorexia nervosa), being contaminated (as in obsessive-compulsive disorder), or having a serious illness (as in hypochondriasis)

E. The worry and physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

F. The symptoms are not due to a substance or a medical condition (eg, hyperthyroidism) and does not occur exclusively during exacerbations of an Axis I disorder (eg, mood disorder, psychotic disorder)

describe avoiding places and activities associated with a prior panic attack.

GAD may be confused with multiple medical entities in which anxiety is often present. Substance-induced anxiety disorders can be confused with GAD. The acute effects of multiple substances can mimic GAD symptoms, including caffeine, nicotine, and stimulants (ephedrine, methylphenidate, amphetamine). Withdrawal from chronically abused substances (ethanol, benzodiazepines) can also mimic GAD symptoms. Other medical entities presenting with some anxiety symptoms include endocrine disorders (associated with elevated thyroid hormone or cortisol or associated with hypoglycemia), cardiac disorders (arrhythmias, congestive heart failure), respiratory disorders (eg, chronic obstructive pulmonary disorder), and neurologic disorders (eg, vestibular dysfunctions). In light of these considerations, an electrocardiogram, thyroid-stimulating hormone measurement, complete blood count, and chemistry panel may be considered in the evaluation of GAD patients. GAD is often comorbid with other psychiatric disorders, including alcoholism, drug dependence, and major depressive disorder [3,10,11]. Thus, when considering a GAD diagnosis, it is essential to probe for these common comorbid conditions.

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**What are treatment options for GAD?**

**Pharmacotherapy**

Effective pharmacotherapy is available for the treatment of GAD. The benzodiazepines were the first class of drugs approved by the U.S. Food and Drug Administration for the treatment of GAD and are the mainstay of short-term anxiolytic treatment. There is a wealth of evidence proving short-term efficacy (< 1 year) of benzodiazepines in GAD [12].

While benzodiazepines are efficacious in the treatment of anxiety, they may cause physical dependence and withdrawal. Abrupt cessation of therapy may result in rebound anxiety or discontinuation symptoms, which have been seen after as little as 4 to 8 weeks of therapy. GAD patients treated chronically with benzodiazepines as monotherapy may have anxiety scale rating scores closer to those of untreated GAD patients than to remitted patients. For this reason, most physicians use benzodiazepines as short-term therapy to treat acute anxiety symptoms [13,14]. Prescription of benzodiazepines for alcohol- or drug-dependent individuals should be avoided when possible because of the potential for abuse.

Antidepressants are also efficacious in GAD [15] but act less quickly than benzodiazepines. Imipramine was the first antidepressant approved for GAD treatment [16,17]. It is not considered a first-line treatment, however, due to its side effect profile. Subsequently, multiple newer antidepressants were approved, including venlafaxine XR, paroxetine, and others. In large-scale studies, venlafaxine XR, a serotonin and norepinephrine reuptake inhibitor (SNRI) [18], demonstrated significantly better clinical efficacy than placebo after 8 weeks [19–23] and after 6 months [24–26] of treatment. Paroxetine was also studied in several GAD trials [22,27,28], with active compound producing significant improvement compared with placebo. More recently, sertraline has also demonstrated efficacy [29,30]. In general, selective serotonin reuptake inhibitors (SSRIs) and SNRIs are effective in treating GAD but require at least 2 weeks to begin to show efficacy. They have multiple advantages over tricyclic antidepressants and benzodiazepines for long-term treatment, including tolerability, safety, and absence of risk for dependence.

The 5-HT1A partial agonists are also approved for treatment of GAD. Of the 5-HT1A partial agonists studied, only buspirone [31,32] has demonstrated consistent anxiolytic properties. Agents such as gepirone [33] or flesinoxan [K. Rickels, unpublished data] have not. In acute double-blind trials, buspirone consistently demonstrated slower onset and slightly weaker overall anxiety efficacy compared with various benzodiazepines [34,35] and antidepressants [19]. For GAD patients who experience intolerable side effects with SSRIs or SNRIs, buspirone is an alternative. In venlafaxine XR studies, patients treated with venlafaxine XR had greater improvement in psychic as compared with somatic (eg, restlessness, muscle tension, palpitations) symptoms relative to patients treated with placebo as measured using the Hamilton Anxiety Scale [36]. Similarly, more favorable responses in psychic as opposed to somatic anxiety were found in paroxetine studies [27] and were also observed earlier with buspirone [31] and with imipramine [17]. Patients whose psychic anxiety is well controlled with antidepressant pharmacotherapy but who have persistent somatic anxiety may benefit from the addition of buspirone and/or a small dose of a benzodiazepine to control the somatic symptoms of anxiety.

The consistency of the results reported for venlafaxine XR and paroxetine suggests that for the short-term (8 weeks) as well as for extended (6 months) treatment of GAD, the SSRIs and SNRIs represent the first-line choice for GAD pharmacotherapy. However, it should be noted that despite the large fraction of GAD patients who respond to acute benzodiazapine therapy or antidepressant therapy, remission rates for GAD remain at around 40% [20,37].

**Cognitive Behavioral Therapy**

Cognitive behavioral therapy (CBT) is considered optimal psychotherapy for GAD [38]. CBT is generally short-term...
therapy, often consisting of 10 to 20 weekly sessions, in which the therapist assists the patient in identifying cognitive distortions and biases in thinking and provides guidance on how to change this thinking. Because benefit is often delayed for weeks, a combination of pharmacotherapy and psychotherapy may be best for most patients. Although there are no long-term (> 1 year) outcome studies of CBT in GAD, short-term benefit of CBT in GAD is comparable to the benefit from pharmacotherapy [38]. Referral to a psychotherapist skilled in CBT should be considered for every GAD patient. A combination of psychotherapy and pharmacotherapy is likely to yield an optimal outcome for most patients.

**Diagnosis**

The physician diagnoses the patient with GAD and prescribes a trial of sertraline 50 mg daily. He also suggests that she try CBT, which has also been shown to be effective for GAD, but the patient declines this treatment.

After taking sertraline for several days, the patient finds that her anxiety is worse and she stops taking the drug.

- **What are the options for treatment in a GAD patient who does not tolerate an SSRI?**

For uncertain reasons, a subset of GAD patients experience an exacerbation of anxiety when started on an SSRI as monotherapy. This may be attributable to the fact that the course of GAD typically waxes and wanes. The exacerbation shortly after starting an SSRI may be coincidence. Sometimes, reassurance is all that the patient needs. Typically, antidepressants require 2 to 3 weeks before symptom improvement is evident.

If an exacerbation in anxiety symptoms occurs after starting an SSRI, the SSRI can be stopped while the patient is treated acutely with a benzodiazepine. For most patients, a benzodiazepine can be well tolerated as chronic monotherapy [39]. However, symptom reduction to an acceptable level with benzodiazepine monotherapy is often not obtained [20,40,41]. If the patient does not achieve adequate symptom reduction with a benzodiazepine after 2 weeks with adequate dosing, an antidepressant can be introduced often without exacerbation of anxiety symptoms. Depending on the patient, the benzodiazepine may be gradually discontinued, beginning several weeks after the antidepressant has been started [42]. The presence of the antidepressant should prevent an exacerbation of anxiety when the benzodiazepine is discontinued as long as the benzodiazepine discontinuation is gradual, occurring over at least 2 to 3 weeks.

**Follow-up**

The physician starts the patient on clonazepam at 0.25 mg twice daily and as needed, with a gradual increase over 1 week to 0.5 mg twice daily and 0.5 mg as needed, depending on symptom severity. The patient reports an approximate 50% reduction in symptom severity within 1 day after starting clonazepam.

The patient continues on this regimen for several weeks. At the next appointment, the patient expresses concern about the long-term addictive potential of clonazepam.

- **Is long-term therapy with a benzodiazepine appropriate in a GAD patient who has an unacceptable increase in anxiety with an antidepressant?**

There are no controlled clinical trials that provide an answer to this question beyond a 6-month time period. However, there is evidence that patients with anxiety disorders do not take more benzodiazepines than needed to control symptoms over a 3-month period [42]. In general, most GAD patients do not achieve remission of symptoms with a benzodiazepine alone [20,37,40,41]. In addition, given the high comorbidity of GAD with substance abuse, long-term therapy of GAD with benzodiazepines should be considered only after consultation with a specialist.

**Follow-up**

After providing some reassurance, the physician prescribes venlafaxine XR 37.5 mg, with a gradual increase to 150 mg daily over 10 days. The clonazepam is continued. The patient reports a further improvement in symptoms after another 2 weeks, at which point she is taking clonazepam 0.5 mg twice daily. The physician recommends that the patient reduce the clonazepam by 0.25 mg every week until the drug is discontinued. The patient tolerates this well, with no increase in anxiety; however, increased severity of symptoms develops over the ensuing 3 months. The clonazepam is reinstated at 0.25 mg twice daily and as needed, with prompt reduction in symptoms.

The patient continues on the venlafaxine XR at 150 mg daily and the clonazepam 0.25 mg twice daily and as needed for the next 6 months. She describes her symptoms as minimal. An attempt to gradually discontinue the venlafaxine XR results in an increase in GAD symptoms, and the dose of 150 mg daily is reinstated. The symptoms remit in 2 weeks. The patient has continued this regimen for several years, with minimal symptoms.

**SUMMARY**

In summary, GAD is a common condition, frequently
presenting in primary care, with considerable costs to society. Effective pharmacotherapy is available, including SSRIs, SNRIs, benzodiazepines, and buspirone. Optimal use of the available agents will improve patient outcomes. Most GAD patients do not achieve remission of symptoms with either a benzodiazepine or an antidepressant alone [17,20,33]. Often, a combination of the 2 classes of psychotropics is more effective that either class alone, although there are no controlled clinical trials that address this issue. CBT is also effective treatment and should be considered for every GAD patient. It should be noted that there are no studies that provide systematic evidence of continued efficacy of antidepressants or benzodiazepines in the chronic (beyond 6–12 months) treatment of GAD. This should be a subject of continued research.

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References


CME EVALUATION: Treatment of Generalized Anxiety Disorder

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following statements about generalized anxiety disorder (GAD) is FALSE?
   (A) Its course tends to be chronic and recurrent
   (B) Onset is usually early in life
   (C) Risk is slightly lower among women
   (D) Remission rates are below 50%

2. Which of the following symptoms or conditions common to anxiety disorders is specific to GAD?
   (A) Fear of embarrassment
   (B) Sleep disturbance
   (C) Global worry unrestricted to a particular situation
   (D) Chronic apprehension
   (E) Comorbid depression

3. Which of the following may present with anxiety symptoms?
   (A) Neurologic disorders
   (B) Respiratory disorders
   (C) Endocrine disorders
   (D) Cardiac disorders
   (E) All of the above

4. Which of the following statements about treatment of GAD is FALSE?
   (A) Benzodiazepine use may lead to physical dependence
   (B) Antidepressants work more quickly than benzodiazepines
   (C) Cognitive behavioral therapy (CBT) is as effective as pharmacotherapy
   (D) Combination therapy may be more helpful than monotherapy

5. A 45-year-old woman presents complaining of constant worry, fatigue, and irritability. She is found to meet diagnostic criteria for GAD. Which of the following treatment approaches would be appropriate?
   (A) Offer referral for CBT
   (B) Begin trial of an SSRI
   (C) Begin trial of an SNRI
   (D) All of the above
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