CLINICAL PRACTICE

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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 authors' clinical recommendations.

A 46-year-old married woman presents with insomnia, headaches, muscle tension, and back pain. She describes a long-term pattern of worrying about several life situations, including health, finances, and her job, and she notes increased anxiety associated with her teenager's leaving home to attend college. She drinks alcohol daily to reduce the tension and help her sleep. In reviewing her history, you note that she has visited your office many times over the past year because of physical symptoms. What do you advise?

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THE CLINICAL PROBLEM

Generalized anxiety disorder is characterized by chronic and persistent worry. This worry, which is multifocal (e.g., about finances, family, health, and the future), excessive, and difficult to control, is typically accompanied by other nonspecific psychological and physical symptoms (Table 1). The term "generalized anxiety disorder" may incorrectly suggest that symptoms are entirely nonspecific, and this misconception may sometimes lead to the inappropriate use of this diagnosis for virtually any anxious patient. A new term — generalized worry disorder — was considered, though not adopted, for the fifth edition of the *Diagnostic and Statistical Manual of Medical Disorders* (DSM-5).[1] However, excessive worry is, indeed, the core and defining feature of generalized anxiety disorder.

According to representative epidemiologic surveys, the estimated prevalence of generalized anxiety disorder in the general population of the United States is 3.1% in the previous year and 5.7% over a patient's lifetime; the prevalence is approximately twice as high among women as among men.[2] The age at onset is highly variable; some cases of generalized anxiety disorder begin in childhood, most begin in early adulthood, and another peak of new-onset cases occurs in older adulthood, often in the context of chronic physical health conditions.[3] Generalized anxiety disorder is, by definition, a chronic disorder; 6 months is the minimum duration of anxiety for diagnosis, and most patients have had the disorder for years before seeking treatment.

Generalized anxiety disorder is particularly prevalent in primary care settings, where it occurs among 7 to 8% of patients.[4] Patients rarely, however, report the symptom of worry. The predominant presentation in primary care (rather than mental health) settings is physical symptoms such as headaches or gastrointestinal distress.[5] In children, generalized anxiety disorder often manifests as recurrent

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Table 1. Criteria for the Diagnosis of Generalized Anxiety Disorder.*

Excessive anxiety and worry about various events have occurred more days than not for at least 6 months.
The person finds it difficult to control the worry.
The anxiety and worry are associated with at least three of the following six symptoms (only one symptom is required in children): restlessness or a feeling of being keyed up or "on edge," being easily fatigued, having difficulty concentrating, irritability, muscle tension, and sleep disturbance.
The anxiety, worry, or associated physical symptoms cause clinically significant distress or impairment in important areas of functioning.
The disturbance is not due to the physiological effects of a substance or medical condition.
The disturbance is not better accounted for by another mental disorder.

* All the features listed must be present in order to make a diagnosis of generalized anxiety disorder. Adapted from the American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.[1]

abdominal pain and other somatic symptoms[6] that may cause them to stay out of school.

Major depression is a common coexisting condition, although major depression may be difficult to distinguish from generalized anxiety disorder because many symptoms of generalized anxiety disorder (e.g., fatigue and insomnia) overlap with those of major depression. Persistent anhedonia (the inability to experience pleasure), which is characteristic of major depression, is not a symptom of generalized anxiety disorder. Patients with generalized anxiety disorder often describe a sense of helplessness, whereas patients with major depression may feel hopeless. Nevertheless, persons with generalized anxiety disorder are at increased risk for deliberate self-harm, including suicide attempts.[7] In many patients, generalized anxiety disorder is an underlying waxing-and-waning condition, with episodic bouts of major depression emerging during particularly stressful life circumstances. This dual occurrence of generalized anxiety disorder and major depression constitutes what is sometimes referred to as "anxious depression," a particularly common clinical presentation in primary care settings.[8]

The differential diagnosis of generalized anxiety disorder is broad. Health anxiety disorder (formerly known as hypochondriasis) is diagnosed when the worries are restricted to a preoccupation with illness. Obsessive–compulsive disorder, which is diagnosed when the ruminations are tied to irrational beliefs (e.g., beliefs about contamination), is often associated with compulsions (such as hand washing). Social anxiety disorder is diagnosed when the fear and worry are constrained to scrutiny by others and embarrassment when the person has to interact with or perform in front of others. In panic disorder, the anxiety is marked by abrupt, unexpected, transient episodes of fear and physical symptoms, and in post-traumatic stress disorder, a history of life-threatening trauma precedes the onset of anxiety, which coalesces around reminders of the traumatic event or events.

Patients with generalized anxiety disorder have increased risks of other mental and physical health conditions (e.g., chronic pain syndromes, asthma or chronic obstructive pulmonary disease, and inflammatory bowel disease).[9] Approximately 35% of people with generalized anxiety disorder self-medicate with alcohol and drugs to reduce the symptoms of anxiety, and this pattern of use is thought to contribute to the increased risk of alcohol- and drug-use problems among these persons.[10] Given the high rates of coexisting conditions, management of generalized anxiety disorder requires attention to a potentially complex array of psychological and physical symptoms, which may be mutually reinforcing.

Well-established risk factors for generalized anxiety disorder include female sex, low socioeconomic status, and exposure to childhood adversity (e.g., physical or sexual abuse, neglect, and parental problems with intimate-partner violence, alcoholism, and drug use).[11] Recent evidence suggests that exposure to physical punishment in childhood is associated with an increased risk of generalized anxiety disorder in adulthood.[12] However, these risk factors are nonspecific and can also be associated with risks of other anxiety and mood disorders.

Studies involving twins have shown evidence of a moderate genetic risk of generalized anxiety disorder, with heritability estimated at between 15 and 20%.[13] Candidate and genome-wide association studies involving persons with generalized anxiety disorder and other anxiety disorders have suggested some genetic associations,[13,14] but these findings have yet to be widely replicated.

A psychological construct known as intolerance of uncertainty — the tendency to react

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KEY CLINICAL POINTS

GENERALIZED ANXIETY DISORDER

- Generalized anxiety disorder is characterized by persistent anxiety and uncontrollable worry that occurs consistently for at least 6 months.
- This disorder is commonly associated with depression, alcohol and substance abuse, physical health problems, or all these factors.
- In primary care, patients with this disorder often present with physical symptoms such as headaches, muscle tension, gastrointestinal symptoms, back pain, and insomnia.
- Brief validated screening tools such as the Generalized Anxiety Disorder 7 (GAD-7) scale should be used to assess the severity of symptoms and response to treatment.
- First-line treatments for generalized anxiety disorder are cognitive behavioral therapy, pharmacotherapy with a selective serotonin-reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (SNRI), or cognitive behavioral therapy in conjunction with either an SSRI or an SNRI. Pregabalin and buspirone are suitable second-line or adjunctive medications.
- Although there is controversy regarding the long-term use of benzodiazepines owing to the potential for misuse and concerns about long-term adverse cognitive effects, these agents can, with careful monitoring, be used on a long-term basis in selected patients with treatment-resistant generalized anxiety disorder.

negatively to situations that are uncertain — has been shown to be a relatively specific characteristic of persons with generalized anxiety disorder.[15] Although it is unclear whether the origin of this construct is experiential or genetic, the observation that a reduction in intolerance of uncertainty is an important mediator of outcomes of cognitive behavioral therapy provides support for its central role in this disorder.[16]

Functional neuroimaging studies involving patients with generalized anxiety disorder have suggested increased activation within parts of the limbic system (e.g., the amygdala) and reduced activation in the prefrontal cortex, with additional evidence of diminished functional connectivity between these regions.[17-19] In addition, preliminary data suggest that effective treatments for this disorder may remediate these functional abnormalities in the brain. For example, functional magnetic resonance imaging in patients with generalized anxiety disorder[20] has shown increased activation of the amygdala while the patients are viewing faces that express emotion, and this activation is attenuated with cognitive behavioral therapy.[21]

STRATEGIES AND EVIDENCE

ASSESSMENT

Patients with generalized anxiety disorder generally have an affirmative response to the question "Do you worry excessively about minor matters?" That question is worth asking of patients with insomnia, a depressed mood, chronic gastrointestinal and other pain symptoms, or other unexplained recurrent health concerns.

Brief questionnaires such as the Generalized Anxiety Disorder 7-Item (GAD-7) Questionnaire[22] (Fig. 1), which take only minutes for the patient to complete, can be used to screen for the disorder as well as to longitudinally monitor outcomes. However, the advisability of routine screening for generalized anxiety disorder remains controversial.

Table 1 lists the DSM-5 diagnostic criteria for generalized anxiety disorder. Patients with suspected generalized anxiety disorder should routinely be asked whether they use alcohol or drugs to reduce anxiety or tension, and they should be screened for depression and the risk of suicide.

MANAGEMENT

Randomized, controlled trials provide strong evidence of the benefits of certain types of pharmacotherapy, psychotherapy, or both for generalized anxiety disorder.[23-25] A stepped-care approach is recommended (Table 2). The initial choice of treatment should depend largely on patient preference (with the majority of patients choosing psychotherapy).[26] Physicians who are not psychiatrists often prescribe medications for and monitor outcomes in these patients; in patients for whom psychotherapy is preferred or pharmacologic management is more complicated, refer-

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Over the past 2 weeks, how often have you been bothered by the following problems? (*Use "✓" to indicate your answer*)	Not at All	Several Days	More Than 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. Having trouble relaxing	0	1	2	3
5. Being so restless that it is 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

Figure 1. Generalized Anxiety Disorder 7-Item Questionnaire.

The total score (0 to 21) is the sum of the individual items. Total scores of 5 to 9 indicate mild, probably subclinical anxiety, and monitoring is recommended. Total scores of 10 to 14 indicate moderate, possibly clinically significant anxiety, and further evaluation and treatment (if needed) are recommended. Total scores of 15 to 21 indicate severe, probably clinically significant anxiety, and treatment is probably warranted. Data are from Spitzer et al.[22]

ral is warranted, but the primary care physician should play a role in encouraging and supporting the patient's therapeutic work with the psychotherapist.

Primary care physicians who are treating patients with generalized anxiety disorder can be supported by a collaborative-care approach that includes the involvement of case managers (e.g., nurses or social workers) who deliver evidence-based psychotherapies and facilitate access to psychiatric consultation when needed. This approach has been shown to be more effective than treatment as usual.[27,28]

Lifestyle Modifications

Before patients embark on a course of pharmacotherapy or psychotherapy, they should be directed to unbiased sources of information about anxiety disorders (e.g., the Anxiety and Depression Association of America; www.adaa.org). Clinical experience and randomized, controlled trials provide support for the prescription of exercise for anxiety, though effect sizes are modest.[29]

Since insomnia is a prominent symptom of generalized anxiety disorder, the patient should be encouraged to practice positive sleep-hygiene behaviors (i.e., to maintain a regular sleep schedule, avoid smoking or the use of nicotine during the evening, and avoid alcohol and the prolonged use of devices with light-emitting screens, such as smartphones, laptops, and television, before bedtime). However, randomized trials are lacking to support specific benefits of sleep hygiene for patients with generalized anxiety disorder.

Pharmacotherapy

Pharmacologic treatment of generalized anxiety disorder results in a reduction in symptoms and disability and improved health-related quality of life.[30] Studies provide support for the efficacy of most (but not all) antidepressants, several benzodiazepines, buspirone, and pregabalin in the treatment of generalized anxiety disorder (Table 3).[31]

Selective serotonin-reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are generally considered to be first-line pharmacotherapies for generalized anxiety disorder, with response rates in the range of 30 to 50%.[23,32] A recent meta-analysis suggested the possibility of publication and reporting biases in clinical trials of these agents for the treatment of anxiety, but the authors concluded that these biases probably did not lead to a systematic inflation of effect sizes.[33] No SSRI or SNRI has been shown to be superior to any other in the

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Table 2. Stepped-Care Approach for Management of Generalized Anxiety Disorder.*

Assessment Phase
Gather a detailed history of symptoms of generalized anxiety disorder and effect on functioning.
Ensure that generalized anxiety disorder is the principal or one of the principal diagnoses.
Evaluate patient for common co-occurring mental health conditions (e.g., depression, other anxiety problems, and substance-use disorders).
Evaluate patient for suicidal ideation, plans, or attempts.
Rule out treatable physical conditions such as thyroid and cardiac problems.
Use the Generalized Anxiety Disorder 7-Item Questionnaire or another suitable measure to gauge severity and track progress.
Step 1. All known or suspected cases of generalized anxiety disorder
Educate patient and family members about generalized anxiety disorder with use of self-help sites (e.g., that of the Anxiety and Depression Association of America [www.adaa.org]).
Educate patient about lifestyle changes that can reduce symptoms of generalized anxiety disorder. Discuss strategies for improving quality and quantity of sleep and encourage regular exercise (such as aerobic exercise and yoga). Encourage patient to minimize caffeine and alcohol use and to avoid nicotine and illicit drugs.
Monitor patient's progress with lifestyle changes.
Step 2. Diagnosed generalized anxiety disorder that has not improved after education and active monitoring in primary care
Suggest low-intensity psychological interventions such as individual nonfacilitated self-help (e.g., books and high-quality websites), individual guided self-help, educational groups, computer-assisted cognitive behavioral therapy.
Step 3. Generalized anxiety disorder with an inadequate response to step 2 interventions
Provide choice of a high-intensity psychological intervention or a drug treatment according to patient's preference and then refer patient for individual or group-based cognitive behavioral therapy (8–16 sessions) or for prescription of first-line pharmacologic treatments (SSRIs or SNRIs).
Step 4. Complex or treatment-refractory generalized anxiety disorder
Refer patient for specialized care by a mental health professional who will prescribe other first-line pharmacologic treatments or adjunctive treatment with a long-acting benzodiazepine (to be avoided among patients who are receiving opioids and among the elderly), buspirone, pregabalin, or quetiapine, and who will consider more intensive cognitive behavioral therapy, other forms of psychotherapy (such as psychodynamic therapy and acceptance and commitment therapy), or both.

* Adapted from United Kingdom's National Institute for Health and Care Excellence guidelines: (www.nice.org.uk/guidance/cg113/chapter/1-recommendations). SNRI denotes serotonin–norepinephrine reuptake inhibitor, and SSRI selective serotonin-reuptake inhibitor.

treatment of generalized anxiety disorder, so the choice of drug should be based on cost and on the patient's prior response to or the physician's familiarity with a particular agent. When SSRIs and SNRIs are used for generalized anxiety disorder, they are administered at the same doses as those used for the treatment of major depression, with the same expectation of time to response (4 to 6 weeks) and with the same precautions and anticipated adverse effects.[34]

The evidence base is growing for the use of SSRIs and SNRIs for the treatment of anxiety disorders, including generalized anxiety disorder, in children and adolescents.[35] However, these medications should be prescribed to children and adolescents only when psychological approaches have failed, and only then by experienced behavioral pediatricians or psychiatrists.

Several randomized, controlled trials have shown a benefit of a newly marketed antidepressant, vilazodone, in patients with generalized anxiety disorder,[36] but this agent has no known advantages over generically available SSRIs or SNRIs. Trials involving patients with generalized anxiety disorder have not consistently shown efficacy of certain other antidepressants, including bupropion and the recently marketed vortioxetine,[37] and these agents are not recommended.

The efficacy of tricyclic antidepressants such as imipramine is similar to that of SSRIs,[32] but tricyclic antidepressants have a less favorable safety profile. Their role in treating generalized

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Table 3. Medications Commonly Prescribed for the Treatment of Generalized Anxiety Disorder.*

Medication	Starting Dose	Target Dose†	Common Side Effects	Comments
	mg/day			
SSRI			Nausea, somnolence, insomnia, jitteriness, diarrhea, sexual dysfunction	
Sertraline	25	100–200		
Paroxetine‡	10	20–60		
Paroxetine CR	12.5	25–75		
Citalopram	10	20–40		Dose should not exceed 40 mg/day because of concerns about prolongation of QT interval
Escitalopram‡	5	10–20		
SNRI			Nausea, somnolence, insomnia, dizziness, sexual dysfunction, hypertension	
Venlafaxine XR‡	37.5	75–225		
Duloxetine‡	20	20–60		
Benzodiazepine			Somnolence, dizziness	Use with caution in the elderly and in patients with past or present substance-use problems; may be used as monotherapy or as an adjunct to SSRI or SNRI
Diazepam	2.5–5.0	10–40		Usually administered in two divided doses
Clonazepam	0.25–0.50	1.0–2.0		May be administered once daily or in two divided doses
Lorazepam	0.5–1.0	1.0–4.0		Usually administered in two divided doses
Alprazolam	1.0–2.0	2.0–6.0		Usually administered in three divided doses
Tricyclic antidepressant			Orthostasis, cardiac arrhythmias, weight gain, potentially lethal in overdose	
Imipramine	10	50–200		
Other medication				May be used as monotherapy or as an adjunct to SSRI or SNRI
Buspirone‡	10–20	20–60	Dizziness, sweating, nausea, insomnia	
Pregabalin	150	150–600	Somnolence, dizziness	Usually administered in two or three divided doses
Gabapentin	100–200	100–1800	Somnolence, dizziness	Usually administered in two or three divided doses
Quetiapine	25	50–200	Somnolence, dizziness, weight gain, and other metabolic side effects	

* This list is not comprehensive. CR denotes controlled release, and XR extended release.
† In older adults, target doses should be at the lower end of the range.
‡ This drug has been approved by the Food and Drug Administration (FDA) for the treatment of generalized anxiety disorder.

anxiety disorder is currently uncertain, though they may be useful in persons who have had a response to them in the past and may be considered in patients who do not have a response to SSRIs or SNRIs.

Referral to a psychiatrist is indicated for patients who do not have a response to SSRIs or SNRIs or who have had adverse effects from these drugs that could not be managed, or when the clinical picture is complicated by a coexisting

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condition (such as a substance-use disorder or suicidality). In such instances, alternative or adjunctive therapies may be prescribed; these include buspirone (a nonbenzodiazepine, nonantidepressant azapirone class of drug that appears to be effective only for generalized anxiety disorder and not for other anxiety disorders),[38] pregabalin (which, although not approved by the Food and Drug Administration [FDA] for generalized anxiety disorder, has been shown to be efficacious in several randomized clinical trials),[39] and quetiapine (also not FDA-approved for generalized anxiety disorder, but its use is similarly supported by data from randomized trials).[40] Treatment with quetiapine or other atypical antipsychotic agents should be undertaken with due regard to the adverse metabolic effects of this drug class and with close monitoring of the patient's weight, lipid levels, and glycated hemoglobin level. Although limited data have suggested efficacy of antihistamines such as hydroxyzine for generalized anxiety disorder, these agents are not recommended because of their tendency to sedate and the absence of longer-term data to support their use.[41]

Benzodiazepines such as diazepam and clonazepam (both of which are long-acting agents) are also efficacious in the treatment of generalized anxiety disorder,[42] but because of concerns about misuse and dependence, some physicians do not administer them for generalized anxiety disorder and other anxiety disorders. Most prescribing guidelines suggest that benzodiazepines should be used only on a short-term basis (3 to 6 months), a time frame that is inconsistent with the typically chronic nature of generalized anxiety disorder. However, many specialists believe that, with close monitoring, benzodiazepines are a reasonable option in selected patients (i.e., those without current or past alcohol-use or other substance-use problems) for whom preferred agents are ineffective or associated with a poor side-effect profile.[23,43] Observational data have raised concern regarding an increased risk of dementia associated with long-term benzodiazepine use,[44] but it is unclear whether this relationship is causal. Benzodiazepines should not be used with opioid medications because of the risk of drug interactions, and the use of these agents should be minimized in the elderly, in whom risks such as falls are likely to outweigh benefits.

Psychotherapy

Randomized, controlled trials have evaluated a number of psychotherapeutic techniques for generalized anxiety disorder, including cognitive behavioral therapy, psychodynamic therapies (which address underlying conflicts that are thought to be the source of anxiety), mindfulness-based therapies (including acceptance and commitment therapy, which encourages a focus on the present and on core values that transcend symptoms and illness),[45] and applied relaxation therapy (which teaches approaches to inducing a relaxed state). Among these forms of therapy, the evidence is strongest for the use of cognitive behavioral therapy in the treatment of generalized anxiety disorder, for which it can be considered a first-line treatment.[25]

The framework of cognitive behavioral therapy posits that patients with generalized anxiety disorder overestimate the level of danger in their environment, have difficulty with uncertainty, and underestimate their capacity to cope. Cognitive behavioral therapy for generalized anxiety disorder involves cognitive restructuring to help patients understand that their worry is counterproductive, exposure therapy to enable patients to learn that their worry and avoidance behaviors are malleable, and relaxation training.

Methods of delivery of cognitive behavioral therapy include weekly individual sessions (60 minutes each for 12 to 16 sessions), 8 to 12 weekly group-based sessions, computer-assisted therapy with minimal assistance from a therapist in primary care, and therapy delivered by means of the telephone in rural areas.[46] These methods have been tested and have been shown to be efficacious, with moderate-to-large effect sizes as compared with the control method (the use of a waiting list).[25]

Whereas cognitive behavioral therapy, which teaches skills to manage anxiety, would be expected to have more durable effects than medications (which stop working when the patient stops taking them), data are lacking from head-to-head trials comparing cognitive behavioral therapy with pharmacotherapy and including long-term follow-up. Patient preference regarding the method of delivery of cognitive behavioral therapy should be assessed. Cognitive behavioral therapy that is fully delivered by means of the Internet may be an ideal starting point for

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some patients,[47] particularly those who do not have ready access to a therapist.

Combined Medications and Psychotherapy

Evidence from randomized trials on the most effective strategy for patients who do not have a response or who have only a partial response to psychotherapy or medication alone is lacking, but practice guidelines recommend the use of combination therapy. In children and adolescents[48] and in older adults,[49] there is some evidence that cognitive behavioral therapy combined with pharmacotherapy yields the best results, though most experts would still recommend starting with cognitive behavioral therapy and sequentially adding pharmacotherapy if needed.

AREAS OF UNCERTAINTY

Although cognitive behavioral therapy and SSRI or SNRI agents are effective in reducing symptoms in up to 50% of patients with generalized anxiety disorder, it remains unclear how best to treat patients who have no response or only a partial response to those therapies. Furthermore, although most experts suggest that patients with generalized anxiety disorder who are treated with medication should continue to receive medication for at least 1 year, the most appropriate duration of maintenance treatment is not known.

Data from randomized trials are lacking to assess the effects of combinations of currently used therapies and also to assess complementary therapies (such as yoga and massage). Data are also lacking on the extent of use, usefulness, and safety of medicinal marijuana for generalized anxiety disorder.

GUIDELINES

Several organizations have published guidelines for the treatment of anxiety disorders, including generalized anxiety disorder; these include the World Federation of Societies of Biological Psychiatry[50] and the Canadian Anxiety Guidelines Initiative Group.[51] The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the case vignette has generalized anxiety disorder and is self-medicating with alcohol to reduce tension. Using a stepped-care approach (Table 2), the physician should perform a careful assessment of her symptoms (with a standardized scale such as GAD-7) and of coexisting conditions, level of disability, and risk of suicide. She should be given information about lifestyle modifications including exercise, sleep hygiene, and reduced caffeine intake and should be strongly advised not to use alcohol to reduce symptoms of anxiety.

Reasonable initial strategies, supported by data from randomized trials, would be to administer an SSRI or an SNRI, refer the patient for cognitive behavioral therapy, or both, with the choice guided by the patient's preference. Benzodiazepines should be avoided, given her pattern of alcohol use to reduce anxiety. Her outcome during treatment should be monitored. If improvement (e.g., a 50% or more decrease in the GAD-7 score, as compared with the pretreatment score) is not seen after 3 months of treatment, a different — or adjunctive — treatment should be offered, and referral to a mental health specialist should be strongly considered if it has not already been recommended.

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