

## Generalized anxiety disorder: Helping patients overcome worry



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### Symptom severity, patient preference help guide treatment selection

**M**rs. M, age 44, is a married mother of 2 who presents to the psychiatric clinic with increased anxiety that recently has become intolerable, stating “I can’t stop my head.” She has experienced anxiety for “as long as I can remember.” She was a shy, anxious child who worried about her parents’ health. Her anxiety worsened at college, where she first sought care. She was prescribed diazepam as needed. The next semester, she had a depressive episode, treated with imipramine, 75 mg/d, which she tolerated poorly.

Mrs. M has received episodic supportive therapy since college. She has been plagued by bouts of anxiety and worry, with insomnia, tension, and fatigue. She worries about financial, career, family, and safety issues and has a phobia of spiders. Her family and friends often comment about her excessive worry, and it has strained her marriage and career; she was passed over for a promotion in part because of her anxiousness. Mrs. M also has experienced several depressive episodes.

Mrs. M has sought medical care for various non-specific somatic complaints; all laboratory tests were normal. Approximately 10 years ago, Mrs. M’s primary care physician prescribed fluoxetine, 20 mg/d, but Mrs. M stopped taking it after a few days, stating she felt “more anxious and jittery.”

To meet DSM-IV-TR diagnostic criteria for generalized anxiety disorder (GAD), patients must experience anxiety and worry that they find difficult to control. The worry and anxiety occur more days than not for at least 6 months and cause clinically significant distress and impairment (*Table 1*).<sup>1</sup> These diagnostic criteria are being reevaluated—the DSM-5 Anxiety Work Group has proposed renaming the condition generalized worry disorder, specifying that only 2 domains need to be

impacted by worry, shortening the required time frame of impairment from 6 months to 3 months, and including at least 1 behavioral change spawned by excessive worry.<sup>2</sup> Although provisional, these recommendations suggest DSM-5 will include changes to GAD when it is published in 2013.

### A common, chronic condition

In the United States, the lifetime prevalence of GAD is 5.7%.<sup>3</sup> It is twice as common in women. Although GAD can occur at any age, 75% of patients develop it before age 47; the median age is 31.<sup>3,4</sup> Patients who present with GAD later in life have a better prognosis.<sup>3,4</sup>

Approximately 90% of GAD patients will meet criteria for another axis I disorder.<sup>3</sup> When GAD patients present for treatment, social phobia and panic disorder are the most common comorbid psychiatric disorders. The lifetime prevalence of a mood disorder among GAD patients is 62%, but as few as 6% of GAD patients will meet criteria for a mood disorder at presentation.<sup>3</sup> The onset of GAD usually precedes depression.<sup>5,6</sup>

Patients with GAD often first seek treatment from their primary care provider.<sup>7</sup> A useful screening tool is the GAD-7 (*Table 2, page 42*).<sup>8</sup> This instrument has a specificity of 92% and sensitivity of 76% for GAD for patients who score  $\geq 8$ .<sup>7</sup> Although the GAD-7 cannot confirm a GAD diagnosis, it can prompt clinicians to conduct a more structured interview. Because higher scores correlate with more severe symptoms, the GAD-7 can be used to measure progress.

### Differential diagnosis

GAD typically has a chronic course with fluctuating symptom severity over the patient's lifespan. Assess patients who present with anxiety for medical conditions that mimic GAD. These include:

- endocrine (hyperthyroidism), metabolic (electrolyte abnormalities), respiratory (asthma), neurologic (seizure disorder), or cardiac (arrhythmia) conditions
- nutritional deficiencies, especially of B vitamins and folate

**Table 1**  
**DSM-IV-TR diagnostic criteria for generalized anxiety disorder**

A) Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)
B) The person finds it difficult to control the worry
C) The anxiety and worry are associated with $\geq 3$ of the following 6 symptoms (with at least some symptoms present for more days than not for the past 6 months): 1) restlessness or feeling keyed up or on edge 2) being easily fatigued 3) difficulty concentrating or mind going blank 4) irritability 5) muscle tension 6) sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D) The focus of the anxiety and worry is not confined to features of other axis I disorders (eg, social phobia, OCD, PTSD, etc.)
E) The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F) The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism), and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder
OCD: obsessive-compulsive disorder; PTSD: posttraumatic stress disorder
Source: Reference 1

- ingestion of substances or medications that may cause anxiety, such as caffeine or amphetamines.

A thorough history, medication review, and physical examination—as well as routine tests such as metabolic panel, complete blood count, thyroid function tests, urine drug screen, and electrocardiography—will capture most of these potential etiologies. In addition to ruling out medical causes, also assess for comorbid psychiatric conditions before reaching a diagnosis.

### Evidence-based treatments

The treatment armamentarium for GAD includes psychotherapy and pharmacotherapy; complementary and alternative

### Clinical Point

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## Generalized anxiety disorder

### Clinical Point

Cognitive-behavioral therapy results in sustained improvements for patients with anxiety

**Table 2**

## Screening for generalized anxiety disorder: The GAD-7

Over the last 2 weeks, how often have you been bothered by any of the following problems?		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.	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

GAD: generalized anxiety disorder

Source: Reference 8

medicine (CAM) modalities may be useful adjunctive treatments. Which approach to use is determined by clinical judgment and the patient's symptom severity and preferences. Combination therapy consisting of psychotherapy and medication often is appropriate.

**Psychotherapy.** Cognitive-behavioral therapy (CBT) is the preferred form of psychotherapy for GAD because it results in sustained improvements for patients with anxiety.<sup>5,9</sup> Other modalities that may be effective include psychodynamic psychotherapy, mindfulness-based therapy, and interpersonal psychotherapy.<sup>10,11</sup>

**Pharmacotherapy.** As few as one-quarter of patients with GAD receive medications at appropriate dose and duration.<sup>12</sup> Antidepressants are a first-line pharmacotherapy.<sup>5</sup> Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors are highly effective for treating GAD.<sup>5</sup> Paroxetine, escitalopram, duloxetine, and venlafaxine are FDA-approved for GAD, but other SSRIs also are used as primary treatment.<sup>5</sup> Assuming the selected agent is tolerable and efficacious, a treatment course of 12 months is recommended.<sup>13</sup>

Benzodiazepines promote binding of the neuroinhibitory transmitter  $\gamma$ -aminobutyric acid and enhance chloride ion influx, thus reducing anxiety. Benzodiazepines have been

widely used because of their rapid onset of action and effectiveness in managing anxiety, but their role in long-term management of GAD is unclear because these medications increase the risk of addiction, cognitive dulling, memory impairment, psychomotor retardation, and respiratory depression when combined with other CNS depressants such as alcohol and opiates. Before prescribing a benzodiazepine, conduct a thorough risk-benefit analysis and obtain informed consent. Long-term benzodiazepine monotherapy is not recommended.<sup>5,14</sup>

Hydroxyzine is an alternative to benzodiazepines.<sup>15</sup> It works as an antihistamine and is FDA-approved for psychogenic neurosis, a Freudian distinction encompassing anxiety derived from psychological rather than physiological factors.

The azapirone buspirone is a non-addictive, generally non-sedating 5-HT<sub>1A</sub> agonist. Although anecdotally some psychiatrists may report limited clinical utility, many analyses found azapirones, including buspirone, were effective for GAD,<sup>16,17</sup> particularly for patients with comorbid depression.<sup>18</sup>

Tricyclic antidepressants are not a first-line choice because of their side effect profile and potential for drug-drug interactions. Nonetheless, some research suggests imipramine may be a reasonable option for GAD.<sup>14,19</sup>

Although not FDA-approved for GAD, anticonvulsant and antipsychotic medica-

tions may be reasonable adjunctive agents for patients with refractory GAD. Studies have suggested gabapentin<sup>20</sup> and quetiapine<sup>21</sup> as options.

**Investigational treatments.** Glutaminergic transmission is being investigated as a target for pharmacotherapy for GAD. In an 8-week, open-label trial, 12 of 15 GAD patients responded to the antiglutamatergic agent riluzole, 100 mg/d, and 8 patients achieved remission.<sup>22</sup> In another study, pregabalin, which promotes calcium channel blockade, significantly reduced patients' scores on the Hamilton Anxiety Rating Scale.<sup>23</sup> However, this medication is a schedule V controlled substance and little is known about its long-term effects. Researchers had proposed that inhibition of corticotropin-releasing factor (CRF) may help reduce anxiety, but in a double-blind, placebo-controlled trial, they found that the CRF antagonist pexacerfont was no more effective than placebo.<sup>24</sup>

**CAM treatments.** A meta-analysis found that compared with placebo, kava extract (*Piper methysticum*) effectively reduced anxiety symptoms.<sup>25</sup> However, considering its risk for hepatotoxicity, kava is not a recommended treatment.<sup>26</sup> Although valerian, St. John's wort, and passionflower have been used to manage GAD, there is insufficient evidence of their effectiveness and safety.<sup>26</sup> No strong evidence supports nutritional supplements such as ginger, amino acids, and omega-3 fatty acids (fish oils) as treatment for GAD. Although there's limited research on resistance training, aromatherapy, yoga, meditation, or acupuncture for treating anxiety, consider these treatments if your patient finds them helpful, because generally they are not contraindicated.

**CASE CONTINUED**

**An antidepressant and CBT**

Mrs. M reluctantly agrees to a trial of sertraline, 50 mg/d. She refuses a prescription for clonazepam because she is afraid of drug dependence but accepts a referral for CBT. Two days later, she calls the clinic and says she is more anxious and wants to stop the sertraline.

**Related Resources**

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**Drug Brand Names**

Bupirone • Buspar	Imipramine • Tofranil
Clonazepam • Klonopin	Paroxetine • Paxil
Diazepam • Valium	Pregabalin • Lyrica
Duloxetine • Cymbalta	Quetiapine • Seroquel
Escitalopram • Lexapro	Riluzole • Rilutek
Fluoxetine • Prozac	Sertraline • Zoloft
Gabapentin • Neurontin	Venlafaxine • Effexor
Hydroxyzine • Vistaril, Atarax	

**Disclosure**

Dr. Barry reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

**Clinical Point**

**Antidepressants are a first-line treatment for GAD; SSRIs and SNRIs are highly effective**

The psychiatrist reassures her and reduces the dosage to 25 mg/d.

Mrs. M's spike of anxiety resolves by her 2-week follow-up appointment and sertraline is titrated to 200 mg/d. Her irritability, anxiety, and mood improve within 2 months. The worry does not completely resolve, but she is much improved at 6 months, and the focus of her therapy shifts to her marriage.

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continued





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### Clinical Point

No strong evidence supports nutritional supplements such as ginger or omega-3 fatty acids for treating GAD

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## Bottom Line

Generalized anxiety disorder is a chronic, highly comorbid condition. Treatment options include psychotherapy (typically cognitive-behavioral therapy) and pharmacotherapy with a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor. Combining psychotherapy with medication is a common approach.