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Treating anxiety without SSRIs

Are SSRI side effects a problem for your patient with generalized anxiety disorder? Here are some options to consider—and others to avoid.

PRACTICE RECOMMENDATIONS

- › Prescribe selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or selected anticonvulsants as first-line treatment for generalized anxiety disorder (GAD). **A**
- › Avoid the use of benzodiazepines for long-term treatment of GAD. **C**
- › Do not recommend valerian, kava extract, or St. John's wort for the treatment of GAD; tell patients there is insufficient evidence of their efficacy. **C**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▶ Brad S, a 39-year-old lawyer, is in your office for a follow-up visit. A month ago, you diagnosed him with generalized anxiety disorder and prescribed paroxetine. Brad reports that the medication worked “like a miracle,” rapidly resolving his constant worry and rumination. Unfortunately, though, he is experiencing a bothersome side effect—sexual dysfunction. He’s having difficulty achieving ejaculation during intercourse and wants to know if you can give him “something else that works just as well.” What would you recommend?

In any given year, about 6.8 million Americans—roughly 3.1% of people ages 18 and older—suffer from generalized anxiety disorder (GAD), according to the most recent national survey of psychiatric illness.^{1,2} GAD is associated with overuse of medical services. In addition, patients with GAD frequently present with somatic illness, typically in primary care settings.³⁻⁵ Women are twice as likely as men to be affected,⁶ and the onset of GAD more commonly occurs at or around midlife, rather than at earlier ages.⁴

Identifying and treating GAD promptly is a high priority, as it exacts a high burden of suffering. Physical and mental comorbidities are extremely common (TABLE). In fact, 66% of those with GAD have at least 1 additional psychiatric condition—most frequently, major depression.⁷

Further evidence of the toll GAD takes comes from the National Comorbidity Survey, a congressionally mandated study of more than 8000 US residents conducted in 1994. Among the respondents, 82% of those who had ever been diagnosed with GAD said they had sought professional help for the disorder, taken medication for it, or found that it interfered with their life or activities “a lot.”⁷

Patients with GAD, like Brad, often start their search for help in primary care. And GAD can usually be treated successfully in such a setting.⁵ Thus, it is crucial for family physicians to not only be on the lookout for signs and symptoms of GAD (See “Is it GAD?” on page 152), but to familiarize themselves with the most effective pharmacological treatments.



The combination of fast onset of action, high efficacy, and lack of sexual side effects makes pregabalin an attractive drug for the treatment of generalized anxiety disorder.

While paroxetine, like other selective serotonin reuptake inhibitors (SSRIs), is well established as a safe and effective treatment for GAD,^{8,9} 1 or more of the most common side effects are often bothersome to patients. These include nausea, reported by 22% of patients; headache, reported by 12% of patients, and abnormal ejaculation/sexual dysfunction, reported by 11% of patients in a study of long-term use of paroxetine for GAD.¹⁰ This review describes the other options you may want to consider—and the ones you'll want to avoid.

Options are numerous, but which is best for your patient?

Many other drug classes and medications are used to treat GAD: tricyclic antidepressants, atypical antipsychotics, serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsants, benzodiazepines, and bupropion, among them. But a number of these options present problems of their own.

Tricyclics, for example, have demonstrated efficacy in treating GAD,¹¹ but are associated with sedation and anticholinergic side effects and are typically not as well tolerated as some other choices. Atypical antipsychotics also have troublesome side effects—primarily, somnolence and weight gain. In addition, atypical antipsychotics require monitoring for rare but life-threatening adverse reactions, such as agranulocytosis,

which limits their practicality in a primary care setting.

Benzodiazepines, while rapidly alleviating feelings of anxiety, have significant withdrawal effects after long-term use. However, they are often used successfully as a short-term treatment for GAD. For that reason, we will include benzodiazepines—along with SNRIs, anticonvulsants, and bupropion—in our discussion of SSRI alternatives for GAD.

SNRIs have high efficacy

Of the 3 SNRIs on the market—desvenlafaxine, duloxetine, and venlafaxine—the latter 2 are approved for the treatment of GAD. Venlafaxine, in particular, has shown great efficacy as both a short- and long-term treatment.¹²⁻¹⁴

A meta-analysis by Meoni et al demonstrated that venlafaxine ER (extended release) provided significantly higher response rates than placebo for the relief of both the psychological and somatic symptoms of GAD.¹³ By week 24 of treatment, the rates of improvement in the treatment group were 66% for psychological symptoms and 67% for somatic symptoms, vs 35% and 47%, re-



TABLE
GAD: Common comorbidities^{7,44}

Psychiatric	Hazard ratio	95% CI
Agoraphobia	19.2	9.1-40.8
Dysthymia	24.8	12.4-49.5
Major depression	13.9	7.9-24.2
Mania	19.6	7.24-53.27
Panic disorder	26.1	9.8-68.2
Substance abuse	1.99	0.68-11.41
Medical	Hazard ratio	95% CI
Atherosclerosis	1.99	0.93-4.13
Cerebrovascular disease	2.95	1.09-3.65
GI	1.40	1.13-1.73
Hypertension	1.33	1.05-1.66
Ischemic heart disease	1.50	1.10-2.04
Respiratory disease	1.28	1.08-1.47

CI, confidence interval; GAD, generalized anxiety disorder; GI, gastrointestinal.

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SSRIs are the gold standard for treatment of GAD, but patients may be bothered by 1 or more common side effects.

spectively, for those in the placebo group. A randomized controlled trial (RCT) by Montgomery et al also found venlafaxine to be well tolerated, with no significant difference in rates of discontinuation due to adverse effects between the SNRI and placebo.¹² (In another study, duloxetine was found to be an effective treatment for GAD, but had a significantly higher dropout rate than placebo.¹⁵)

Venlafaxine has some of the same adverse effects as the SSRIs, however; commonly reported side effects include nausea, dizziness, and somnolence,^{12,16} as well as a significant incidence of sexual side effects.^{14,17} For this reason, venlafaxine would not be the best choice for Brad. It might, however, be an option for a patient who is bothered by sedation or weight gain caused by SSRIs.

Anticonvulsants: A newer option for anxiety

Anticonvulsants have been used only re-

cently to treat anxiety disorders—an indication for which this class of drugs has not received approval. The mechanism of action appears to involve suppression of neuronally activated “fear circuits” in the amygdala and hippocampus. These circuits are part of the autonomic output that occurs when someone initially experiences fear, and when he or she reexperiences the fear in a nonthreatening setting. Periodic or chronic overactivation of these circuits may lead to panic attacks, GAD, and other anxiety disorders.¹⁸

Anticonvulsants suppress neuronal activation through a variety of mechanisms, including gamma-aminobutyric acid stimulation (valproate), sodium channel blockade (carbamazepine, phenytoin), and calcium channel blockade (pregabalin). Although a variety of anticonvulsants have been tested as a treatment for GAD, pregabalin is the only 1 that multiple RCTs have found to be effective.¹⁹⁻²² In an RCT comparing pregabalin, lorazepam, and placebo, both pregabalin and lorazepam decreased anxiety scores significantly more

than placebo. Pregabalin was better tolerated than lorazepam and had the added benefit of not being associated with withdrawal effects upon discontinuation of the drug. In addition, pregabalin showed efficacy compared with placebo in as little as 1 week.²²

In another RCT comparing pregabalin, venlafaxine, and placebo, Montgomery et al showed that both pregabalin and venlafaxine were superior to placebo.²³ Pregabalin had a faster onset of action than venlafaxine (1 vs 2 weeks) and was better tolerated.

Doses of pregabalin used in clinical trials ranged from 150 mg to 600 mg daily, given in divided doses.²⁴ In clinical practice, physicians are advised to start at the lower dose and titrate upward until either an effective dosage is reached or side effects become bothersome.

Common side effects of pregabalin include dizziness (8%-45%), somnolence (4%-28%), weight gain (up to 16%), and edema (up to 16%). Thrombocytopenia occurs in 3% of patients; other blood dyscrasias are rare.²⁵ Laboratory monitoring is not routinely indicated, and neither sexual side effects nor gastrointestinal disturbances are commonly reported.²⁵

With evidence indicating that GAD is a chronic, recurrent disease,²⁶ long-term efficacy is important. One RCT found that long-term use of pregabalin (24 weeks) maintained remission of symptoms more effectively than placebo.²⁷

The combination of fast onset of action, high efficacy, and lack of sexual side effects makes pregabalin an attractive drug for the treatment of GAD, especially for patients who cannot tolerate SSRIs. However, cost may be a consideration. Unlike SSRIs, pregabalin is not available as a generic. At a discount retailer such as Costco, the per-pill cost of pregabalin 150 mg (typically taken twice a day) is \$2.45; in contrast, paroxetine 20 mg (generally taken only once daily) is 40 cents per pill. In addition, pregabalin is a class V controlled substance, and little is known about its long-term effects.

CASE 1 ▶ Pregabalin makes sense for Brad. After discussing SSRI alternatives with Brad, he decides to switch to pregabalin, despite

the higher cost. He makes an appointment for the following month. At that visit, you're pleased to see that Brad is feeling better and happy with the treatment choice he has made. Your next GAD patient, however, is a more difficult case.

CASE 2 ▶ Janet W, a 60-year-old patient whom you "inherited" from a former partner, has been taking alprazolam 1 mg tid for many years for "excessive nervousness." She frequently complains about lack of energy and weight gain, but resists any suggestion that she discontinue alprazolam. "I can't function without something to calm my nerves," Janet says.

Benzodiazepines as a "bridge"

Benzodiazepines have long been established as effective in treating anxiety symptoms. Because of their fast onset of action, drugs in this class are often used as a "bridging strategy," to give rapid relief from symptoms while another medication, typically an SSRI, is started and titrated.

A 2005 meta-analysis comparing benzodiazepines with placebo for short-term treatment of GAD showed the drugs to be superior to placebo in reducing anxiety symptoms. Patient satisfaction with benzodiazepines was high, as evidenced by a significantly lower dropout rate among those in the benzodiazepine group (20.5%), compared with the placebo group (30.2%).²⁸ Typical side effects are somnolence and weight gain.

There is ample evidence that long-term benzodiazepine use produces tolerance and severe withdrawal effects. Discontinuing benzodiazepines after long-term use (>3 months) can be challenging, with patients reporting irritability, insomnia, and anxiety. Several strategies to ease the withdrawal process have been explored.

A 2000 RCT compared the overlapping use of imipramine or buspirone vs placebo when tapering patients off their long-term benzodiazepine regimen.²⁹ The study found that patients who took imipramine before and during their benzodiazepine taper were significantly more likely to discontinue their benzodiazepines compared with those using placebo. Successful discontinuation for

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The SNRI venlafaxine has shown great efficacy for both the short- and long-term treatment of GAD.

those using buspirone—a 5-HT_{1A} receptor agonist—approached statistical significance.²⁹ (Buspirone has also been studied as a primary treatment for GAD, and found to have a relatively small effect and a side effect profile that includes dizziness, nausea, and asthenia.³⁰ And there is preliminary evidence that bupropion XL may be as efficacious as escitalopram in treating GAD, with both drugs being well tolerated.³¹)

Another study focusing on the discontinuation of benzodiazepines found that adding cognitive behavioral therapy (CBT) to a gradual taper regimen significantly improved patients' chances of complete cessation. Seventy-five percent of patients receiving CBT stopped taking benzodiazepines, compared with 37% of patients in the placebo-plus-taper group.³²

CASE 2 ▶ After educating Janet about the risks of continued long-term use of benzodiazepines, you propose a plan to enable her to decrease her dose of alprazolam over many weeks. It involves a referral to CBT to give Janet the opportunity to find nonpharmacologic

ways of managing her anxiety, and a prescription for imipramine 75 mg daily, which she would take while she tapers her benzodiazepine use at a rate of 25% per week. Reluctantly, Janet agrees.

At her 1-month follow-up, Janet reports that she has followed the tapering schedule, but that she frequently feels nervous and is having trouble sleeping. She states that she does not want to be dependent on drugs, and asks if there is a natural treatment to calm her nerves.

What to tell patients about “natural” alternatives

Patients may express a preference for “natural” treatments for GAD, and ask about valerian, kava extract, or St. John's wort (hypericum). All 3 are available in the United States and marketed for the treatment of anxiety and insomnia (valerian), depression (hypericum), and as a euphoric (kava).

■ **Valerian.** A Cochrane review found insufficient evidence to draw any conclusion about the efficacy of valerian for the treatment of GAD because of the paucity of RCTs available for review.³³ The single RCT found to be acceptable for review had a small sample size (N=36) and showed no significant difference in symptom reduction among the valerian, diazepam, and placebo groups.³⁴

■ **Kava extract.** Cochrane published a systematic review of kava extract in 2002, including a meta-analysis of 5 RCTs.³⁵ The meta-analysis showed a significant reduction in the Hamilton Anxiety Scale (HAMA) score for kava users vs placebo, although the effect size was small. The authors of this meta-analysis chose to exclude a 2002 RCT by Connor et al³⁶ because that study used a different kava preparation than the others. However, Connor found that kava extract was not superior to placebo in reducing anxiety symptoms as measured by the HAMA, and inclusion of this study would have reduced the meta-analysis conclusion to borderline significance.

In addition, there are serious concerns about the association of kava with hepatotoxicity, including liver failure.³⁷ According to the National Center for Complementary and Alternative Medicine (NCCAM), there is some

Is it GAD?

Signs and symptoms of generalized anxiety disorder (GAD) include excessive, and largely uncontrollable, worry; tension or restlessness; fatigue; difficulty concentrating; irritability; muscle tension; and sleep disturbances, lasting for at least 6 months.⁴⁵ But GAD is associated with a wide range of physical and psychiatric comorbidities, and patients frequently present with somatic complaints, as well.

A medical history and physical exam to look for causes, comorbidities, and conditions that mimic GAD is an important first step when you suspect that a patient has an anxiety disorder. The differential diagnosis for GAD includes hyperthyroidism and Cushing's disease, arrhythmias, anginal symptoms, pheochromocytoma, mitral valve prolapse, and excessive caffeine intake.⁴⁶

Screening for major depression, the most common psychiatric comorbidity, and for alcohol and drug use is indicated, as is a medication history. Prescription medications or illicit drugs (and even some over-the-counter products) may be the cause of anxiety symptoms, or be surreptitiously used to alleviate them.

evidence that kava may be beneficial in treating anxiety.³⁸ However, NCCAM-funded studies of kava were suspended after the US Food and Drug Administration issued a warning in 2002 about a link between kava supplements and the risk of severe liver damage.^{38,39}

■ **St. John's wort.** There are case reports of the efficacy of St. John's wort—commonly used as an alternative treatment for depression—in the treatment of GAD.^{40,41} NCCAM is conducting studies of this supplement for a broader spectrum of mood disorders.⁴² Because of the lack of robust evidence of its effectiveness in treating GAD, however, the authors of a review article urged physicians not to recommend St. John's wort as a treatment for anxiety.⁴³

CASE 2 ▶ You discuss “natural” alternatives with Janet, explaining that they are lacking in evidence of efficacy, and slow her tapering schedule, which minimizes her rebound symptoms. Eventually, Janet

is able to reduce her benzodiazepine use to occasional prn dosing, and to discontinue her use of imipramine. At a follow-up visit 6 months later, she reports that she feels more energetic and mentally alert since she discontinued regular use of the benzodiazepine.

CASE 1 ▶ Brad stays on pregabalin with minimal sedation, no sexual dysfunction, and marked improvement in his GAD. “I hate the idea of taking medication every day, but this really works,” he says. At a follow-up visit about a year later, you ask Brad whether he would like to continue treatment. He reports that the drug is working well, and he is reluctant to stop taking it. “This has made a big improvement in my life,” Brad says. **JFP**

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Using imipramine or buspirone—or CBT—as part of a benzodiazepine taper increases the likelihood of achieving complete cessation.

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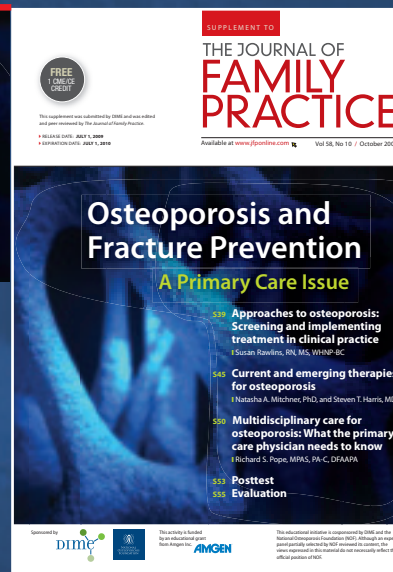
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