

Pharmacotherapy of Generalized Anxiety Disorder

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Less than one third of people afflicted with generalized anxiety disorder (GAD) experience spontaneous remission, and the symptoms of GAD wax and wane throughout a person's life. The burden of GAD may be reduced with psychopharmacologic therapy. The medications with the most evidence of efficacy in GAD are the benzodiazepines, including a new long-acting formulation of alprazolam. These drugs have a low incidence of side effects but may cause physical dependence, withdrawal, and sedation. Antidepressants are also efficacious in GAD but act less quickly than benzodiazepines. Tricyclic antidepressants such as imipramine may substantially reduce symptoms of anxiety but are not considered a first-line therapy because of their side effects spectrum. The extended-release formulation of venlafaxine and selective serotonin reuptake inhibitors such as paroxetine and sertraline are also efficacious in GAD. While their association with sexual dysfunction may be intolerable for some adults, these drugs may be more appropriate than the benzodiazepines because their chronic use does not lead to dependence. Buspirone also significantly reduces symptoms of GAD and is associated with less sexual dysfunction than SSRIs and less sedation than benzodiazepines. Combining antidepressant and benzodiazepine therapy or medication treatment and psychotherapy may lead to an increase in improvement in patients not responding to 1 treatment approach alone. The most effective treatment for managing the recurrent symptoms of this chronic disorder will remain unknown until more long-term studies using both drug and nondrug therapies are conducted. Remission rates are still only about 40%, signifying the need for improved treatment interventions.

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Generalized anxiety disorder (GAD) is a persistent, impairing disease. In GAD, remission is generally defined as a score ≤ 7 or an improvement of 70% on the Hamilton Rating Scale for Anxiety (HAM-A), while clinical response is defined as a 50% improvement in symptoms from baseline on the HAM-A or moderate or marked improvement as determined by the Clinical Global Impressions-Improvement scale (CGI-I).¹ Although many patients in medication trials for GAD, which are usually short-term, have not achieved remission, the number and severity of their symptoms have been significantly reduced with anxiolytic treatment. When choosing a pharmacologic treatment for GAD, physicians should consider each anxiolytic medication's evidence of efficacy and the patient's symptom severity, duration of illness, comorbidity, ability to tolerate the medication's side effects, and previous treatment history.

CHARACTERISTICS OF GAD

The term *generalized anxiety disorder* first appeared in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III),² when psychoneurotic anxiety, a disorder in DSM-II,³ was split into GAD and panic disorder. The DSM-III also added the duration criterion of at least 1 month. In DSM-IV,⁴ the required duration of illness was extended to ≥ 6 months. In a recent worldwide study in primary care settings using the 10th revision of the *International Classification of Diseases (ICD-10)*,⁵ Maier et al.⁶ observed a prevalence rate of 8%.

According to DSM-IV criteria, individuals with GAD have uncontrollable, excessive anxiety or worry (apprehensive expectation) about several events during more days than not for at least 6 months. This anxiety and worry must be associated with at least 3 of the following 6 somatic symptoms: restlessness, fatigue, irritability, difficulty concentrating, muscle tension, and sleep disturbance. This combination of anxiety, worry, and physical symptoms must cause substantial distress or impair social, occupational, or other important areas of functioning and not be the result of another Axis I disorder or be related to a medical condition such as hyperthyroidism or substance abuse.

In addition to patients who meet these full criteria for GAD, there are even more patients who suffer from sub-threshold GAD symptoms, which are often diagnosed according to DSM-IV as anxiety not otherwise specified,

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acute stress disorder, or adjustment disorder with anxious mood. Many of these patients may not be given a diagnosis of GAD according to DSM-IV because these criteria require that symptoms must have been present for at least 6 months and that worry and anxiety are excessive and uncontrollable. However, many of these same patients may be given a GAD diagnosis if the less stringent diagnostic criteria of the ICD-10, which do not have an extended duration criterion and do not require excessive symptoms and worry as a primary complaint, are used.⁷

Two thirds of individuals with GAD may have 1 or more comorbid psychiatric disorders.⁸ Therefore, GAD may be a consequence of or a risk factor for other psychiatric disorders. In the National Comorbidity Survey, which used DSM-III-R criteria, Wittchen and colleagues⁸ found that about 38% of individuals with GAD may also have another anxiety disorder, and about 48% may have comorbid depression. Wittchen et al.⁸ also found that at least 10% of the population with GAD also had a comorbid panic disorder, phobia, or substance abuse and dependence disorder. This high rate of comorbidity seems to affect the severity and treatment of GAD. Among those individuals with GAD and a comorbid psychiatric disorder, 84% thought GAD had greatly interfered with their activities, sought professional help for GAD, or took medication for the disorder, while only 59.2% of individuals who had GAD without a comorbid psychiatric disorder met 1 of these criteria.

Patients who have GAD with and without a comorbid disorder seem to experience comparable somatic symptoms. In a study comparing 28 GAD patients without comorbidity with 77 GAD patients with comorbid psychiatric disorders, Brawman-Mintzer and colleagues⁹ found no significant differences in levels of somatic anxiety between both GAD groups. The majority of individuals in each group experienced the 6 symptoms listed in the DSM-IV criteria for GAD: restlessness, muscle tension, fatigue, irritability, difficulty sleeping, and difficulty concentrating. In addition, most individuals had trembling or shaking, nausea/diarrhea or abdominal distress, clammy hands, dry mouth, and a tendency to startle. Although not affected by comorbid psychiatric disorders, the severity of somatic symptoms may differ from patient to patient, even in patients who have comparable levels of psychic symptoms.¹⁰

The impairment associated with GAD leads to high treatment, productivity, and mortality costs. While studies have not separated the costs of GAD from the costs of other anxiety disorders, the total cost of all anxiety disorders in the United States in the 1990s was estimated to be \$42.3 billion.¹¹ Of these costs, 54% were attributed to non-psychiatric medical treatment, 31% to psychiatric treatment, and 2% to pharmaceutical costs. Additional costs attributed to the workplace and mortality were 10% and 3%, respectively. The costs of GAD may be related to the per-

sistence of the disorder. The symptoms of GAD frequently wax and wane throughout a patient's life, and less than one third of patients with GAD experience a spontaneous remission.¹ With appropriate psychotherapeutic and medication treatment, the patient's symptomatology and its associated economic burden to society are clearly reduced.

PHARMACOLOGIC OPTIONS

Once GAD, including GAD at the subthreshold level, has been diagnosed, the physician must establish clear treatment goals for both target symptoms and duration of therapy. Physicians should also create a supportive and collaborative relationship with their patients; they should present the benefits and risks of each medication and consider the patients' concerns regarding treatment. Medications should be prescribed at the lowest effective dose to minimize side effects, yet at the highest dose necessary to cause not only improvement but also remission. In addition to pharmacotherapy, patients with GAD may benefit from counseling by mental health professionals on how to manage their anxious feelings and worry. Medications are not a panacea that solves all problems. Depending on the medication chosen, after the first 4 to 8 weeks of treatment, the physician and patient should be able to make a preliminary assessment of the drug's efficacy and adverse effect profile. A lack of improvement should cause the physician to consider both the diagnosis and the treatment regimen used. The physician may increase the patient's daily dose, shift to another medication, or consider augmentation treatment. If long-term medication therapy appears indicated, the patient's treatment response should be regularly assessed. While intermittent (p.r.n.) therapy may be appropriate for some patients, continued therapy, lasting for months, may be the best choice for many chronically anxious patients. Treatment should be discontinued by gradual tapering and followed by medication-free periods.

Benzodiazepines

Benzodiazepines have more evidence of safety and efficacy than any other medication in GAD.¹² Several benzodiazepines, including those with short half-lives such as alprazolam¹³⁻¹⁶ and lorazepam^{17,18} as well as those with long half-lives such as clorazepate¹⁹ and diazepam,²⁰⁻²² have been found efficacious in randomized, double-blind, placebo-controlled trials, some of which have compared different benzodiazepines. In an early double-blind trial¹³ that used DSM-III criteria, 151 anxious nonpsychotic patients were randomly assigned to 4 weeks of treatment with alprazolam, diazepam, or placebo. When the improvement in patients' symptom severity was measured on the HAM-A and the CGI-I, the alprazolam and diazepam groups were comparable and had significantly lower 4-week symptom scores than placebo (Table 1).

Table 1. Improvement With Alprazolam, Diazepam, and Placebo in 151 Patients With GAD (LOCF dataset)^a

Measure	Week 4			p Value
	Alprazolam Group	Diazepam Group	Placebo Group	
HAM-A total score ^b	9.5	11.2	16.7	.005 ^c
Global improvement (% with marked or moderate)	76	77	32	.001

^aData from Rickels et al.¹³ Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward.

^bThe baseline HAM-A total score was 24.2.

^cAlprazolam and diazepam compared with placebo.

Another randomized, double-blind trial²³ compared the efficacy of bromazepam, a benzodiazepine not marketed in the United States, and the extended-release (XR) formulation of alprazolam in patients with modified DSM-III-R GAD. Patients received 3 mg t.i.d. of bromazepam or 2 mg h.s. of alprazolam XR for 21 days, and doses were then tapered over 1 week. Alprazolam XR and bromazepam had a rapid onset of action and comparable efficacy. Both treatment groups experienced substantial reductions in their mean HAM-A scores from baseline, and more than 70% of patients in each group responded to treatment, that is, had marked or moderate improvement in CGI-I scale scores. Adverse events and discontinuation-related effects for both drugs were generally mild. The advantage of alprazolam XR was that it needed to be taken only once per day.

When prescribing benzodiazepines, physicians should consider their efficacy in GAD and side effect profiles. Benzodiazepines have a rapid onset of action and are usually well tolerated. These drugs reduce somatic symptoms of anxiety earlier than psychic symptoms,^{22,24} and, contrary to some physicians' prescribing practices, for patients who do not respond within the first 2 weeks of benzodiazepine treatment, further treatment is contraindicated. For patients who do respond to benzodiazepine therapy, the most common side effects, which are generally mild or moderate and frequently only temporary, include sedation, sweating, dizziness, loss of appetite, headache, and ataxia. In addition, central nervous system side effects may occur less frequently with alprazolam XR than immediate-release formulations of benzodiazepines because alprazolam XR has lower peak blood level concentrations.²⁵ The use of alcohol and other central nervous system depressants with benzodiazepines is contraindicated and may significantly increase the side effects of benzodiazepines. The use of these drugs should be limited to acute treatment (i.e., 2–4 weeks) to prevent the development of dependence on therapeutic doses.²⁶ Benzodiazepines may be prescribed p.r.n., and if several acute courses are indicated, they should be interrupted by 2 to 4 weeks of benzodiazepine-free periods.

Table 2. Guide to Length of Benzodiazepine Taper as a Function of Duration of Treatment^a

Length of Treatment	Length of Taper
2 wk	0–2 d
4 wk	0–2 wk
8 wk	2–3 wk
6 mo	4–8 wk
≥ 12 mo	2–4 mo

^aAdapted from Rickels et al.²⁷ A swift taper allows better separation between rebound anxiety/withdrawal and relapse than does an extended taper.

About 40% to 80% of patients treated with benzodiazepines for 4 months or longer experience a discontinuation, or withdrawal, syndrome. This discontinuation syndrome occurs with all benzodiazepines, whether they have long or short half-lives.²⁶ During benzodiazepine discontinuation, patients may experience both rebound and withdrawal symptoms.

The recommended length of the taper depends on the duration of treatment, the daily dose of the benzodiazepine, the drug's half-life, and the patient's acceptance of stopping benzodiazepine treatment (Table 2). Switching from a benzodiazepine with a short half-life to one with a long half-life is not needed unless a relatively swift taper is planned. Taper should be gradual, with the first half of the taper taking much less time than the second half. An exception to this guideline is that patients who were treated for only up to 4 weeks with long half-life benzodiazepines, such as clorazepate or clonazepam, may have their medication tapered over only 1 week. Patients who have used benzodiazepines for over 1 year should begin to taper their medication only after their level of psychopathology has been aggressively treated and reduced to a minimum by treatment with various drugs or nondrug therapies, appropriate to the patient's psychopathology. For patients who received more than 10 mg/day of diazepam or an equivalent dose of another benzodiazepine (e.g., ≥ 2 mg of lorazepam or ≥ 1 mg of alprazolam) for a year or more, the daily dose should initially be tapered to 10 mg of diazepam or an equivalent dose, and only after 1 to 2 additional months of maintaining this dose should the dose be gradually lowered to zero. The final taper attempt may last 4 to 8 weeks.²⁷

Because rebound and withdrawal symptoms reach their peak toward the end of the taper and usually disappear within the first few weeks after treatment is stopped, a period of 2 to 4 weeks free of benzodiazepines is needed to distinguish these symptoms from relapse that would necessitate another course of anxiolytic treatment.

One of the keys to a successful taper is to establish a collaborative and cooperative relationship with the patient. Physicians should warn patients to expect some discomfort, and they should not attempt to taper patients' medication during periods of uncontrolled medical illness or seri-

ous family, social, or work stress. To reduce rebound anxiety and withdrawal symptoms, physicians may coprescribe psychotropic medications such as imipramine, trazodone, carbamazepine, valproate, buspirone, or a selective serotonin reuptake inhibitor before, during, and after the benzodiazepine taper.^{27,28} In addition to adjuvant medication, extra support and an extended taper period may be helpful for patients who have personality problems such as neuroticism or passive dependency.²⁹ Insomnia may be treated with sedating antidepressants or antihistamines,²⁷ and cognitive therapy has also been found to help patients who are tapering their benzodiazepine medication.³⁰

5-HT_{1A} Partial Agonists

Buspirone, an azapirone, has been effectively used to treat GAD since the 1980s. In an analysis of data from 6 double-blind, placebo-controlled, 4-week trials of buspirone in 427 patients with GAD, Feighner and Cohn³¹ found that HAM-A scores were significantly lower for patients treated with buspirone than for those treated with placebo. Several studies have found that buspirone and benzodiazepines, such as diazepam,³²⁻³⁵ clorazepate,¹⁹ lorazepam,^{18,36} and alprazolam,¹⁴ may have comparable efficacy significantly superior to that of placebo in relieving the symptoms of GAD. Although the onset of action is slower for buspirone than for benzodiazepines,^{14,19,33} patients who have taken buspirone may maintain improvement in GAD symptoms longer than patients treated with benzodiazepines.¹⁹ Buspirone appears more effective in treating psychic rather than somatic symptoms of anxiety.^{31,32} In addition, buspirone's efficacy in depression with significant degrees of anxiety may make this drug suitable for patients who have GAD and comorbid depression.³⁷ However, the efficacy of buspirone may be decreased by recent benzodiazepine treatment.³⁸

Usually the side effects of buspirone, which may include gastrointestinal problems, excitement, dizziness, headache, nervousness, and light-headedness, are rated as only mild to moderate.³⁹ This drug may also be associated with less sexual dysfunction than other anxiolytics⁴⁰ and with less sedation than the benzodiazepines.³⁹ Patients on buspirone therapy who have recently taken benzodiazepines may experience more side effects than patients who have not recently received benzodiazepine treatment.³⁸

Tricyclic Antidepressants

Imipramine is the only tricyclic antidepressant (TCA) studied in GAD that has consistently produced significantly higher improvement rates than placebo.^{22,41} The study by Rickels et al.²² on imipramine, diazepam, and trazodone in GAD provided the impetus for a worldwide program to study antidepressants in this disorder. The authors demonstrated that imipramine, while having a slower onset of action than diazepam, was more effective than diazepam after 8 weeks of treatment. Hoehn-Saric et al.²⁴

found that imipramine also had a slower onset of action than alprazolam but was as effective as the benzodiazepine by week 6. These 2 studies^{22,24} also found imipramine to be more effective in reducing the psychic than somatic symptoms of anxiety.

In Germany, the tricyclic compound opipramol is often used to treat anxiety. Recently, Möller and colleagues¹⁶ conducted a randomized, double-blind, placebo-controlled trial of opipramol, alprazolam, and placebo in 307 patients with ICD-10 GAD. When HAM-A scores after 28 days of treatment were adjusted for baseline, both opipramol and alprazolam reduced the mean HAM-A score significantly ($p = .02$ and $p = .004$, respectively) more effectively than placebo.

TCAs are generally associated with more disturbing adverse events than benzodiazepines,^{22,24} and the most common side effects of TCAs, dry mouth, drowsiness, dizziness, constipation, and weight gain, may frequently keep patients from adhering to a prescribed medication regimen. In contrast, taking imipramine before, during, and after benzodiazepine discontinuation has been shown to reduce symptoms of rebound and withdrawal associated with benzodiazepine discontinuation and, therefore, significantly improves patients' success in tapering benzodiazepine treatment.²⁸

Selective Serotonin Reuptake Inhibitors

Of the selective serotonin reuptake inhibitors (SSRIs) that have been studied in GAD, presently only paroxetine has been approved by the FDA for the treatment of this disorder. Paroxetine, at a daily dosage of 20 to 50 mg, was found to be significantly more effective than 2'-chlorodesmethyldiazepam⁴² and placebo⁴²⁻⁴⁴ in reducing HAM-A and Sheehan Disability Scale scores in 8-week, randomized, controlled trials. In addition, treatment for 4 to 6 months with paroxetine has been associated with marked improvement in the harm avoidance and self-directedness measures of the Temperament and Character Inventory.⁴⁵

While paroxetine is the SSRI that has been studied most extensively in GAD, studies have also shown fluvoxamine and sertraline to be efficacious in reducing the severity of GAD symptoms. A large multisite, 10-week investigator-initiated study (O. Brawman-Mintzer, M.D.; M.R.; K.R.; et al., unpublished data, 2002) that was recently completed observed significantly more improvement with sertraline than placebo in GAD. Sertraline was also found to be more effective than placebo in reducing scores on various pediatric rating scales and the HAM-A in a study⁴⁶ on children with GAD. In addition, fluvoxamine⁴⁷ was found to improve Pediatric Anxiety Rating Scale scores significantly more than placebo in children suffering from acute anxiety disorders, including primarily social anxiety disorder but also GAD and separation anxiety disorder.

The side effects of paroxetine and other SSRIs—except central serotonin syndrome, which may occur if an SSRI is combined with other serotonergic agents—are usually mild and include nausea, dry mouth, sedation, asthenia, headache, sexual dysfunction, and constipation. Although SSRIs should be tapered to avoid mild discontinuation symptoms, these drugs are not associated with significant sedation or physical dependence. Therefore, they may represent a more appropriate treatment than benzodiazepines for children and adolescents with GAD.

Serotonin-Norepinephrine Reuptake Inhibitors

The extended-release (XR) formulation of the serotonin-norepinephrine reuptake inhibitor venlafaxine, which is approved by the FDA for the treatment of GAD, has been studied in both short-term^{48,49} and long-term^{50,51} trials. These studies showed that 75, 150, or 225 mg/day, but not 37.5 mg/day, of venlafaxine XR consistently reduced the scores on the HAM-A significantly more than placebo, with a trend for the highest improvement occurring with 225 mg/day. In an 8-week, multicenter, randomized, double-blind, placebo-controlled trial of 405 patients with DSM-IV GAD, Davidson et al.⁴⁹ observed significantly ($p \leq .05$) more improvement with venlafaxine XR than with buspirone in the patient-completed Hospital Anxiety and Depression (HAD) anxiety subscale score but not in the HAM-A total score. In a 6-month, multicenter, randomized, double-blind, placebo-controlled trial of 238 patients with DSM-IV GAD without concomitant major depressive disorder, Gelenberg et al.⁵⁰ reported that venlafaxine XR at doses of 75, 150, or 225 mg/day produced significantly ($p < .001$) more improvement in HAM-A total scores than did placebo. In a European, 6-month, multicenter, randomized, parallel-group study, Allgulander et al.⁵¹ compared 37.5, 75, and 150 mg/day of venlafaxine XR with placebo. The symptoms of patients taking the 75- or 150-mg/day doses, but not the 37.5-mg/day dose, showed significantly ($p < .05$) greater response as measured by the HAM-A total and psychic anxiety factor scores and the HAD than placebo.

The most common short-term adverse events associated with venlafaxine XR are nausea, somnolence, dry mouth, dizziness, sweating, sexual dysfunction, constipation, and anorexia. However, some of these symptoms may subside with treatment. Gelenberg et al.⁵⁰ found that the only adverse events reported in 10% or more of the patients who had taken venlafaxine XR for at least 56 days were dizziness, nausea, and sexual dysfunction.

Combination Therapy

For patients who do not respond well to treatment with a single medication, a combination of 2 medications or of medication and psychotherapy may be appropriate. One recommended combination of medication for GAD is augmenting antidepressant (e.g., SSRI) therapy with benzo-

diazepines for 3 to 4 weeks until the antidepressant becomes effective and then tapering the benzodiazepine dose over a 1-week period.⁵² Because of their early onset of efficacy, benzodiazepines will relieve acute anxiety symptoms more quickly than antidepressants and have the ability to counteract potential adverse events such as agitation associated with antidepressant therapy in some patients. In addition, a benzodiazepine such as alprazolam XR that remains at an effective blood level between doses⁵³ may further reduce the re-emergence of anxiety symptoms.

The most extensively studied psychotherapy in GAD is cognitive-behavioral therapy (CBT), which several randomized controlled trials⁵⁴⁻⁵⁸ have reported to be efficacious in minimizing the symptoms of GAD. Six months after patients participate in CBT, recovery rates may be as high as 50%,⁵⁹ and improvements gained with CBT may be maintained 12 months after therapy is discontinued.^{54,55} Although some doubts exist about the long-term efficacy of psychotherapy in GAD,⁶⁰ the combination of psychotherapy and an anxiolytic may, in some patients, lead to more improvement and reduced relapse rates than medication treatment alone.⁵⁸

TREATMENT ALGORITHMS

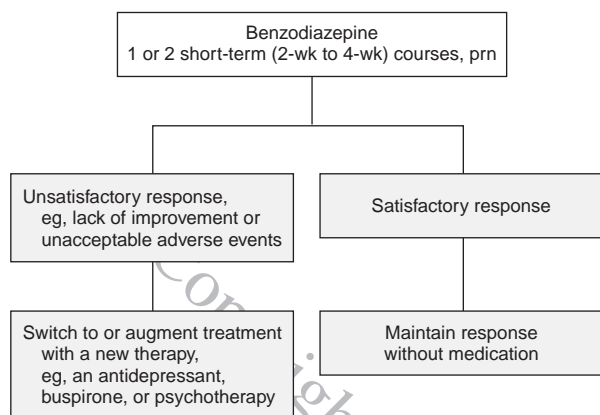
The symptoms of GAD, while often chronic, do frequently wax and wane. Therefore, some patients may benefit from short, intermittent courses of anxiolytic therapy.⁶¹ These patients include those suffering from double anxiety, i.e., patients who have a constant low level of trait anxiety but occasionally experience an acute exacerbation of anxiety,⁶² and patients whom Akiskal⁶³ describes as suffering from “anxious temperament.” Acute symptoms of GAD may be treated with 1 or 2 short (i.e., 2-week to 4-week) courses of benzodiazepine treatment, interrupted by 2-week to 4-week periods of no treatment. Because benzodiazepines have a rapid onset of action, these drugs are more appropriate than buspirone or antidepressants for treatment intended to last for only a few days or weeks (Figure 1).

If more prolonged treatment of GAD seems indicated, the antidepressants and buspirone are considered today to be the treatments of choice as they do not cause physical dependence, a troubling finding with chronic use of benzodiazepines (Figure 1). The same recommendation holds true for those patients who do not respond to 1 or 2 short courses of intermittent benzodiazepine therapy. Of the newer antidepressants, paroxetine and venlafaxine XR have been approved by the FDA for the treatment of GAD, but the efficacy of other antidepressants such as imipramine²² and sertraline (reference 46 and O. Brawman-Mintzer, M.D.; M.R.; K.R.; et al., unpublished data, 2002) has also been established in GAD.

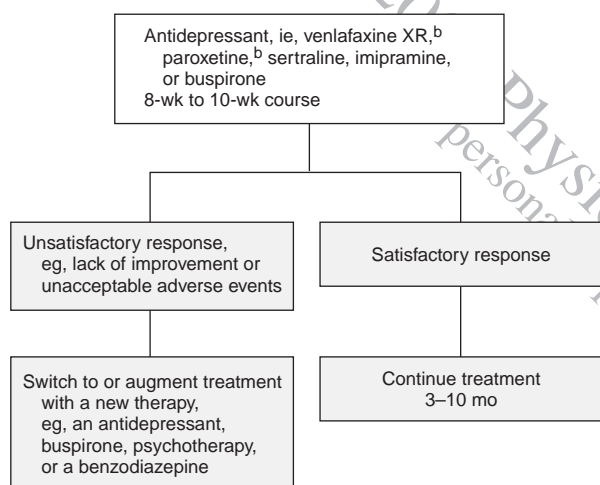
Patients who do not respond to treatment with a single agent, if treatment has been provided for a sufficient pe-

Figure 1. Medication Treatment Algorithms for GAD^a

Algorithm A. Subthreshold GAD Symptoms With a Short Duration



Algorithm B. Full-Threshold, Chronic, DSM-IV GAD



^aData from Rickels and Schweizer.⁶¹ Abbreviation: GAD = generalized anxiety disorder.

^bApproved by the U.S. Food and Drug Administration for the treatment of GAD.

riod of time and at the highest tolerable dose, may either be switched to another medication, to psychotherapy, or to a combination of either 2 medications or medication and psychotherapy. For example, benzodiazepines are frequently combined with SSRIs during the first 4 weeks of treatment of several anxious conditions to produce early efficacy and give the SSRIs time to work.

Many clinicians recommend treatment periods of up to 1 year for patients suffering from chronic GAD symptoms.¹ However, this recommendation is not yet supported by long-term, double-blind relapse studies. For long-term treatment of chronic symptoms, benzodiazepines are usually offered only if none of the other treatment choices, including psychotherapy, were found to be effective and/or tolerable to the patient. Whether prolonged medication

treatment, lasting at least 6 months, will increase remission rates in GAD from the usual rate of 35% to 40% obtained after acute treatment has yet to be established. For example, in studies^{50,51} of venlafaxine XR, remission rates did not increase significantly over a 6-month treatment period. A study¹⁹ conducted with clorazepate and buspirone found that 70% of patients completing 6 months of treatment remained well for at least 4 weeks; however, after 1 year of follow-up,⁶⁴ over 50% of patients were again in need of anxiolytic therapy.

CONCLUSION AND RECOMMENDATIONS

The best method to manage GAD over patients' lifetime has yet to be established. Some patients will clearly require vigorous, long-term drug treatment.⁶⁵ Yet, for many patients, reaching remission is still an unobtainable goal. Only about 60% to 70% of patients report moderate or marked improvement after 8 weeks of acute anxiolytic therapy, and only about 35% to 40% of those patients experience full remission. All medications that are efficacious in GAD do frequently cause adverse events that some patients find unacceptable. Therefore, it is important for the physician to have a variety of anxiolytics available when treating anxious patients with medication.

Many physicians and patients express concern about prescribing or taking anxiolytic medication over the long term. Yet, international experts⁶⁵ agree that anxiolytics such as antidepressants and benzodiazepines are both safe and effective in the short-term and long-term treatment of GAD. Benzodiazepines are preferred for the short term (3 to 4 weeks), and buspirone and antidepressants such as venlafaxine XR, paroxetine, imipramine, and sertraline are preferred for the long term (≥ 6 weeks). Very little is presently known about relapse and remission rates obtained after more than 10 weeks of therapy. The few studies that have been conducted for 6 months do not seem to support an increase in remission rates.^{19,50,51} Antidepressants are particularly good treatment choices for anxious patients with significant comorbid symptoms of depression, even if these symptoms do not fulfill the diagnosis of major depressive disorder.²² Finally, while benzodiazepines are the treatment of choice for only short-term and acute treatment, these drugs, nevertheless, may have to be considered as treatment options for those chronically anxious patients who have experienced unacceptable adverse events or have not yet achieved the desired level of improvement with prolonged treatment of several different medications and psychotherapy. If the chronic use of benzodiazepines is considered a necessity, it is important to discuss with the patient the risks involved with long-term benzodiazepine treatment before initiating therapy.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), carbamazepine (Eptol, Tegretol, and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others),

diazepam (Diastat, Valium, and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine XR (Effexor XR).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, imipramine and sertraline are not approved by the U.S. Food and Drug Administration for the treatment of generalized anxiety disorder.

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