

Refractory Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) has a lifetime prevalence in the US population of about 5.7%. Typically, GAD begins in early adulthood and tends to have a chronic and persistent course. The disorder frequently presents comorbidly with other conditions, and about 90% of patients with GAD have at least 1 comorbid lifetime psychiatric disorder. Patients with GAD tend to be high users of medical services; the disorder is associated with significant physical as well as psychological symptomatology and impacts health, family relationships, and employment. Pharmacologic and psychosocial treatments are available for GAD. Different side effect profiles, speed of onset of action, and discontinuation requirements of individual drugs need to be taken into account when selecting treatment. Treatment selection should include consideration of comorbidity, psychological function, social impairment, and refractoriness, as well as the need for ongoing intervention for many individuals. Innovative treatments, including anticonvulsants, atypical antipsychotics, and others, as well as treatment targeting concomitant insomnia, may help improve outcomes for affected individuals.

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Generalized anxiety disorder (GAD) is a chronic and disabling psychiatric disorder, the treatment of which involves consideration of comorbidity, psychological function, and social impairment. Innovative treatments may be required to achieve full recovery, and ongoing intervention may be needed to maintain benefit.

Prevalence

The epidemiology of GAD is discussed in more detail by Weisberg¹ elsewhere in this supplement, but according to the most recent National Comorbidity Survey,² the lifetime prevalence of GAD is 5.7%. As is true for most mood

and anxiety disorders, women tend to be affected by GAD more than men in about a 2:1 ratio.²

Generalized anxiety disorder is the most common anxiety disorder and is among the most common psychiatric disorders overall in the general medical setting.³ In primary care patients from 14 countries, the mean 1-month prevalence of GAD as defined by the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* was 7.9%.⁵ Among primary care patients who complained of any anxiety problems, 22% were found to have GAD.⁶ Further, up to about one fifth of high utilizers of medical care have GAD⁷; and the somatic symptoms associated with the anxiety disorder often cause individuals to seek medical evaluation and treatment. Elsewhere in this supplement, Culpepper⁸ describes the increased use of health care services by patients with GAD.

While rates of GAD tend to rise until middle age and then plateau among men, the prevalence of GAD in women keeps increasing (Figure 1).⁹ The reasons for this increased prevalence in older women are unclear, but the rise may be due, in part, to hormonal changes associated with the perimenopausal period as well as psychosocial changes associated with aging.

Diagnosis

The cardinal feature of GAD is excessive and uncontrollable worry that lasts for most of the day for 6 months or more. Other anxiety symptoms associated with GAD include feelings of restlessness, easy fatigability, trouble concentrating, irritability, muscle tension, and sleep disturbance. Although the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*¹⁰ diagnostic criteria for GAD require 6 months or more of persistent symptoms,

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- ◆ Effective pharmacologic and psychosocial treatments for generalized anxiety disorder (GAD) are available.
- ◆ Many patients with GAD remain symptomatic despite standard interventions.
- ◆ Alternative and novel strategies are needed to manage refractory anxiety and improve outcomes for many individuals with GAD.

many patients have already experienced symptoms for years when they seek anxiety treatment; further, patients with even shorter durations of symptoms that otherwise meet criteria for GAD, experience comparable degrees of impairment and distress.¹¹

Neurobiology

The underlying neurobiology of GAD and other anxiety disorders is becoming better understood. As noted by Stein¹² elsewhere in this supplement, one study¹³ showed that children and adolescents with generalized anxiety had increased right-sided and total amygdala volumes compared with those of control subjects, a finding consistent with the role of the amygdala in fear and pathologic anxiety. In GAD subjects compared with controls, greater volume of the superior temporal gyrus was noted, as was greater right-to-left asymmetry.¹⁴ The superior temporal gyrus is also involved in higher cognitive processing of fear and modulation of amygdala function.¹⁵ These studies^{13,14} suggest some right hemispheric involvement in anxiety, and a variety of abnormalities in the amygdala and superior temporal gyrus early in the lives of individuals with GAD, consistent with the idea that people may be born with a biologic predisposition to anxiety. Other influences, including developmental and environmental influences, may in part determine whether this vulnerability or predisposition to anxiety is expressed.

Course

Typically, GAD is a chronic disorder with a waxing and waning course; the majority of affected individuals do not experience prolonged remission.⁶ Patients may require innovative treatments to achieve full recovery and ongoing treatment to maintain benefit. Treating patients to full recovery is critical.¹⁶ One study¹⁷ demonstrated that treated individuals who were improved but not fully recovered had higher rates of relapse than those who attained full remission (Figure 2). Long-term treatment is often necessary; as many as 25% of patients who stopped treatment relapsed within 1 month, and up to 80% of patients relapsed within 1 year of stopping treatment.¹⁸

Comorbidity

Generalized anxiety disorder typically presents comorbidly with other disorders. The National Comorbidity

Survey⁹ indicated that 90.4% of patients with GAD had at least 1 other lifetime psychiatric disorder; 62.4% of these individuals had a lifetime history of comorbid depression, and 23.5% to 35.1% had other anxiety disorders. More than a third (37.6%) had a history of alcohol abuse, and 27.6% had a history of drug abuse. Other data¹⁹ suggested that 17% of individuals with GAD had comorbid bipolar disorders. Stein,¹² Weisberg,¹ and Simon²⁰ address comorbidity in more detail elsewhere in this supplement.

Attention to comorbid disorders is critical when selecting treatment for GAD. For example, alcohol or substance abuse issues need to be addressed, and, if possible, administration of benzodiazepines should be avoided in patients with a substance abuse diathesis.²¹ In patients with anxiety and bipolar disorder, administration of antidepressants may cause affective lability and should be avoided, or if necessary, antidepressants should be administered concomitantly with mood stabilizers.^{22,23}

CONSEQUENCES OF GAD**Utilization of Health Care Services**

Patients with GAD are high utilizers of medical services.⁶ Compared with control populations, the mean number of primary care visits over 12 months was about double for individuals with GAD or with GAD and depression compared to nonaffected individuals (7.2 for controls, 13.8 for GAD, and 14.6 for GAD with depression).⁶

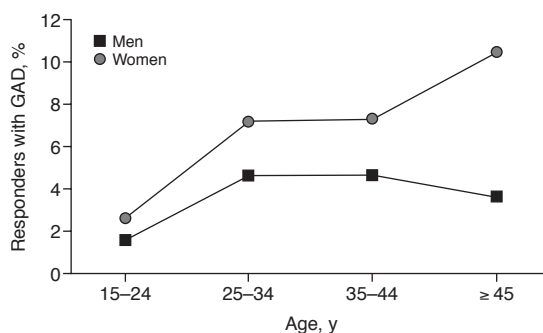
Physical Well-Being

The presence of anxiety can have a negative impact not just on an individual's psychological function but also on his or her physical well-being. For instance, as Culpepper describes elsewhere in this supplement,⁸ GAD is an independent risk factor for coronary heart disease²⁴ and may represent a significant risk factor for increased cardiac morbidity and mortality. Although the hypothesis that treatment of anxiety will have a salutary effect on reducing adverse cardiac outcomes is a reasonable one, a relative paucity of systematic data addresses this issue.

Social and Economic Impact

Generalized anxiety disorder is associated with substantial psychosocial impairment. One study²⁵ noted that about one fourth of individuals with GAD did not marry.

Figure 1. Lifetime Prevalence of DSM-III-R GAD According to the National Comorbidity Survey Database^a



^aData from Wittchen et al.⁹
Abbreviations: DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; GAD = generalized anxiety disorder.

Further, about 20% to 30% of individuals with GAD or panic disorder received welfare or disability payments.²⁵ Among individuals with GAD, 7% had attempted suicide, with 15% of those with GAD and comorbid MDD making an attempt.²⁵ A recent large-scale epidemiological study²⁶ demonstrated that the association of GAD with increased disability and impairment is comparable to that of major depression and greater than that of substance use disorders, personality disorders, and other anxiety disorders.

Generalized anxiety disorder is associated with decreased productivity in the workplace, resulting in substantial social and economic costs to both individuals and society in general. According to one study,⁶ an individual with pure GAD lost an average of 6 work days per month. Further, 34% of patients with GAD reported at least a 10% reduction in work productivity, and about 11% reported at least a 50% decrease in work activity. The cost to the U.S. economy of lost work days and reduced work productivity caused by anxiety disorders was estimated to be over \$4 billion a year.⁶

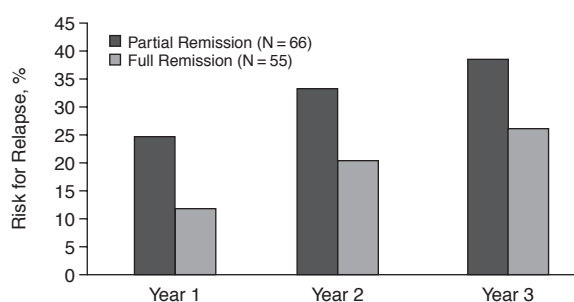
TREATMENT CHOICES AND REFRACTORY GAD

Given the prevalence of GAD and its noxious impact on individuals, treatment is critical. A variety of treatment strategies, both pharmacologic and psychosocial, appear to be effective. Each strategy has advantages and disadvantages, and some standard interventions may be particularly appropriate for individuals with refractory GAD. First-line treatment with many of the drugs discussed here is covered by Davidson elsewhere in this supplement.²⁷

Pharmacotherapy

Benzodiazepines. Benzodiazepines are effective interventions for the treatment of GAD and have been used for this purpose for decades. They have the advantages of a short latency of therapeutic onset and a generally favor-

Figure 2. Probability of Relapse Over 3 Years in Patients With GAD After Partial or Full Remission^a



^aData from Yonkers et al.¹⁷ Full remission = Psychiatric Status Rating Scale (PSR) score = 1 or 2 for 8 consecutive weeks; partial remission = decrease in symptoms to PSR score of 3; relapse = increase in PSR score to 5 or 6 (full criteria) for 2 weeks. Abbreviation: GAD = generalized anxiety disorder.

able side effect profile. Benzodiazepines can be used on an as-needed basis for situational anxiety as well as for ongoing therapy. Clinical experience suggests they may also be useful as augmentation for patients remaining symptomatic despite initial antidepressant treatment for GAD, although this assertion has not been subjected to much systematic study.

Benzodiazepine administration may have some drawbacks. Side effects include sedation, cognitive and psychomotor impairments in some individuals (older patients are at particular risk), and negative interactions with alcohol. Individuals who take benzodiazepines on a regular basis for several weeks can develop physiologic dependence, and should have the drug tapered slowly when discontinuing to decrease potential withdrawal symptomatology.

Given the high rate of comorbid depression in individuals with GAD, it is important to recognize that benzodiazepines alone are generally not effective for GAD with comorbid depression. Clinicians should assess patients with GAD for depression to ensure that those patients with both disorders are also treated with antidepressants. A study²⁸ of individuals with GAD who were treated with the benzodiazepine diazepam, the tricyclic antidepressant imipramine, or placebo showed that, in individuals with minimal levels of depression, both the antidepressant and the benzodiazepine were effective in reducing anxiety symptoms compared with placebo. However, in individuals with more significant depression, although the antidepressants remained effective for reducing anxiety symptoms, the benzodiazepine did not. These results underscore the importance of avoiding, when possible, monotherapy with benzodiazepines in anxious patients with significant depression.

Individuals with a predisposition to abuse alcohol and other substances may abuse benzodiazepines, but people without an alcohol or drug abuse history rarely abuse these agents or escalate their use to high doses. Consistent with

this assertion is a study²¹ examining data from 2,440 Medicaid patients who received benzodiazepines for a variety of conditions for at least 2 years. Throughout the study, doses remained low (ie, equivalent to about 10 mg/d of diazepam), and the rate of escalation to a high dose of benzodiazepines was only 1.6%.

Tricyclic antidepressants. A study²⁸ by Rickels and colleagues demonstrated the efficacy of the tricyclic antidepressant imipramine for GAD. However, tricyclic antidepressants are not as widely used now as they were in the past because of their greater side effect burden relative to that of the newer classes of antidepressants.

Azapirones. Buspirone, a 5-HT_{1A} partial agonist, affects serotonin and dopamine receptors, and several studies^{29,30} have demonstrated its benefit for individuals with GAD.

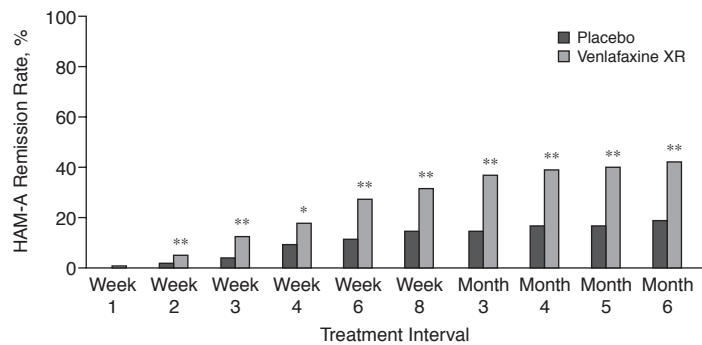
However, its effectiveness in practice has been less consistent and robust than hoped. Currently, buspirone is relatively rarely used as monotherapy; however, it may be useful as augmentation to first-line agents for patients with panic disorder, GAD, or social phobia, and comorbid depression, as well as for individuals with sexual dysfunction because of antidepressants.

SSRIs and SNRIs. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are effective for the treatment of GAD, and some including paroxetine,³¹ escitalopram,³² venlafaxine extended-release (XR),³³ and duloxetine³⁴ have U.S. Food and Drug Administration (FDA) approval for this indication.

The SSRIs and SNRIs are generally better tolerated than older classes of antidepressants such as the tricyclic antidepressants and monoamine oxidase inhibitors and are effective against comorbidities that commonly occur with GAD, particularly comorbid depression. However, like all antidepressants, the SSRIs and SNRIs take at least 2 to 3 weeks to begin to exert significant therapeutic effect and further, have the potential to increase anxiety early in treatment.³⁵ In addition, unlike benzodiazepines, the SSRIs are not effective for acute situational anxiety, and their use may be associated with a variety of problematic side effects, including sexual dysfunction and weight gain. The SSRIs and SNRIs share generally similar potential side effect profiles, although venlafaxine may be associated with a dose-related risk of increased blood pressure, and duloxetine may be associated with an increased risk of urinary retention.

Both SNRIs and SSRIs have been found to be effective for long-term treatment of GAD. For instance, escitalopram was significantly more effective than placebo in a relapse prevention study over 76 weeks in patients with

Figure 3. Time Course of Remission Rates for Venlafaxine XR and Placebo in GAD (LOCF)^a



^aReprinted with permission from Montgomery et al.³³ Remission = HAM-A Total Score \leq 7.

* $P < .05$.

** $P < .001$.

Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, XR = extended release.

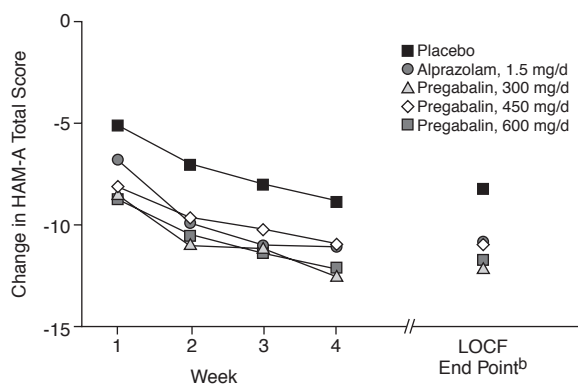
GAD (relapse rates 19% vs 56% respectively, $P < .001$).³² In addition to reducing relapse, as patients remain on medication therapy, ongoing treatment is associated with a greater degree of improvement over time (Figure 3).³³ For example, Montgomery et al.³³ reported that 61% of patients taking venlafaxine XR for GAD who had responded but not remitted by week 8 of treatment had reached remission after 6 months, compared with 39% of those taking placebo.

Treatment-Refractory GAD

Although antidepressants and benzodiazepines represent efficacious first-line strategies for the treatment of GAD, many patients receiving them remain somewhat symptomatic or fail to respond at all. A clear need remains for additional effective agents and interventions for patients who are persistently symptomatic. Relatively few systematic data address optimal strategies for the management of GAD refractory to initial therapeutics. However, the existing data and clinical experience suggest that alternative or augmentative use of benzodiazepines added to antidepressants, anticonvulsants, atypical antipsychotics, and other agents, as well as cognitive-behavioral therapy (CBT), are reasonable strategies to consider after weighing their associated risk profiles.

Anticonvulsants. Pregabalin is an $\alpha_2\delta$ Ca⁺⁺ channel modulator that acts as a presynaptic modulator of several excitatory neurotransmitters. It is not indicated for treatment of GAD in the United States, although it is indicated for this use in Europe. Pregabalin demonstrated efficacy for GAD in several large randomized controlled trials (RCTs)^{36–38} in which it was more effective than placebo and had comparable efficacy and speed of onset to a benzodiazepine comparator (Figure 4). Gabapentin, a compound structurally related to pregabalin, has been described in

Figure 4. Efficacy of Pregabalin Versus Alprazolam or Placebo in Reducing Anxiety Symptoms in Patients With GAD^a



^aReprinted with permission from Rickels et al.³⁶

^bAt LOCF end point, vs placebo, $P < .001$ for pregabalin, 300 mg/d; $P = .02$ for pregabalin, 450 mg/d, and alprazolam, 1.5 mg/d; and $P = .002$ for pregabalin, 600 mg/d.

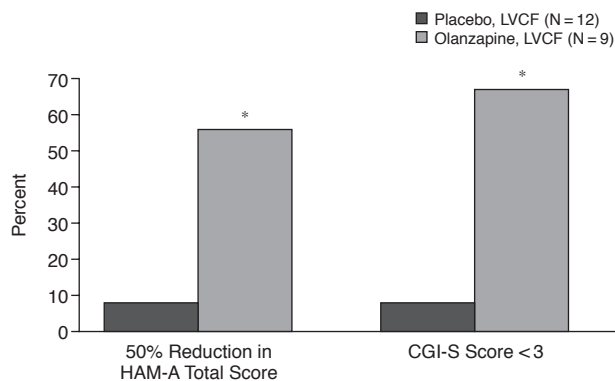
Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward.

case reports³⁹ as potentially effective for GAD, although this has not been assessed in RCTs. The potential anxiolytic efficacy of both pregabalin and gabapentin for GAD in the presence of significant major depression is uncertain.

Tiagabine is a selective γ -aminobutyric acid (GABA) reuptake inhibitor that increases synaptic GABA availability. Although tiagabine demonstrated efficacy in one RCT,⁴⁰ subsequent combined analysis of 3 additional RCTs⁴¹ failed to show benefit for the drug, and did not support consideration of it as a generally effective anxiolytic.

Antipsychotics. First-generation antipsychotics have been used as anxiolytics for many years, and trifluoperazine received FDA approval for short-term treatment of nonpsychotic anxiety.⁴² However, concern about the potential of first-generation antipsychotics to cause extrapyramidal symptoms and tardive dyskinesia has limited their use in practice. Second-generation or atypical antipsychotics have a lower propensity to cause extrapyramidal symptoms or tardive dyskinesia than the older agents and have a variety of effects on serotonin receptors believed potentially relevant to anxiolysis. As a result, there has been interest in the use of these agents for the treatment of GAD. Augmentation with olanzapine (Figure 5),⁴³ and risperidone⁴⁴ for the treatment of patients with GAD remaining symptomatic despite standard anxiolytic therapy was positive in small RCTs, although negative in a larger trial with risperidone.⁴⁵ Adjunctive aripiprazole^{46,47} and ziprasidone monotherapy⁴⁸ were effective for refractory GAD in open-label trials, and there have been positive⁴⁹ and negative⁵⁰ augmentation trials with quetiapine as well. Further,

Figure 5. Augmentation With Olanzapine Versus Placebo in Refractory GAD After 6 Weeks of Fluoxetine Treatment^a



^aData from Pollack et al.⁴³

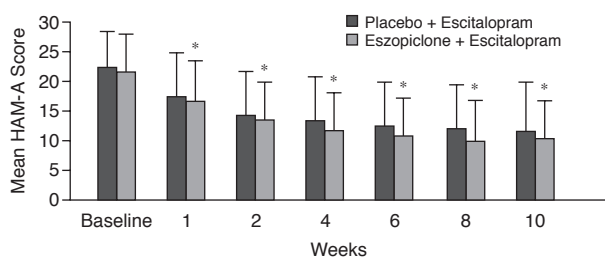
* $P < .05$.

Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, LVCF = last visit carried forward.

quetiapine demonstrated potential efficacy in several large short- and long-term RCTs of acute and maintenance monotherapy in nonrefractory GAD, and it is currently under review at the FDA for these indications. Atypical antipsychotics are generally used at lower doses for the treatment of GAD (eg, 2.5–10 mg/d olanzapine, 0.5–3 mg/d risperidone, 2–15 mg/d aripiprazole, 50–300 mg/d quetiapine) compared to doses used in psychotic disorders. The onset of therapeutic effect with atypical antipsychotics is often within the first week or 2 after initiation of treatment. Although the second-generation antipsychotics have less (though not absent) propensity to cause extrapyramidal effects (compared with the older antipsychotics), their use may be associated to varying degrees with a variety of adverse effects including weight gain, hyperglycemia and diabetes, elevated lipids, and other manifestations of metabolic syndrome. Recommendations for baseline and ongoing monitoring of patients treated with second-generation antipsychotics have been published and should be reviewed by clinicians employing these agents.⁵¹

Riluzole. Based on preclinical and clinical evidence for abnormalities with regulation of the excitatory neurotransmitter glutamate in patients with anxiety, riluzole, a presynaptic glutamate release inhibitor used in the treatment of amyotrophic lateral sclerosis, has been studied in patients with GAD. An 8-week, open-label, fixed-dose trial⁵² of riluzole in 18 outpatients with GAD resulted in significant ($P < .0001$) reduction in anxiety symptoms; 67% of patients responded and 44% entered remission by week 8. Side effects included insomnia, nausea, sedation, and dry mouth; transient elevation of liver function test values occurred in some patients. Although this agent is unlikely to be widely used for GAD because of its high cost, examination of other agents with effects on the

Figure 6. Effect of Escitalopram Plus Eszopiclone or Placebo on Anxiety in Adults With GAD and Insomnia^a



^aReprinted with permission from Pollack et al.⁵⁴

* $P < .05$.

Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety.

glutamatergic system may be a promising avenue for future drug development.

Eszopiclone. Sleep disturbance occurs in many individuals with GAD. Recent evidence suggests that, similar to effects reported in depression,⁵³ directly targeted treatment of insomnia may have a salutary effect on anxiety as well as sleep symptoms. In a double-blind, 10-week study,⁵⁴ patients with GAD were treated with the SSRI escitalopram for all 10 weeks and were randomly assigned to additional treatment with the hypnotic eszopiclone ($n = 294$) or placebo ($n = 301$) for 8 weeks; during the last 2 weeks, those who had taken eszopiclone received placebo. Sleep and daytime functioning improved significantly ($P < .05$) in the individuals who received the hypnotic compared with those who received placebo, and the patients who received the hypnotic also experienced significant reduction in Hamilton Rating Scale for Anxiety scores that persisted even after the specific sleep item in the scale was removed ($P < .05$; Figure 6). After discontinuation of the hypnotic, rebound insomnia did not appear and treatment differences in anxiety (though not sleep) measures were maintained.

Psychosocial Therapies

In addition to pharmacologic treatments, psychosocial interventions, including CBT, have shown efficacy in the treatment of GAD. Cognitive-behavioral therapy targets maladaptive thoughts, feelings, and behaviors. Patients learn alternative patterns of response to anxious thoughts and develop coping strategies. A review⁵⁵ of data on psychological therapy suggested significant benefit for GAD from individual CBT or individual applied relaxation, which produced recovery in 51% and 60% of patients, respectively. In comparison, open-ended, analytically oriented psychotherapy led to recovery in 4% of patients. In practice, CBT may be a useful augmentation strategy to pharmacotherapy, but the evidence is equivocal and relatively slight, and further work is needed to evaluate this issue.

CONCLUSION

Generalized anxiety disorder is prevalent and associated with significant distress and impairment. In practice, most patients with GAD have comorbid conditions, including mood disturbance, other anxiety disorders, or substance abuse. Effective pharmacologic and psychosocial treatments are available, but many patients remain symptomatic despite standard interventions. Alternative and novel strategies are often needed to manage refractory anxiety and improve outcomes for many individuals with GAD.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), buspirone (BuSpar and others), diazepam (Valium and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), quetiapine (Seroquel), riluzole (Rilutek and others), risperidone (Risperdal and others), tiagabine (Gabitril), venlafaxine (Effexor and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, alprazolam, aripiprazole, diazepam, eszopiclone, fluoxetine, gabapentin, imipramine, olanzapine, pregabalin, quetiapine, riluzole, risperidone, tiagabine, and ziprasidone are not approved by the US Food and Drug Administration for the treatment of generalized anxiety disorder.

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