Treating Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is characterized by chronically persistent worry and therefore requires effective long-term treatment. This article reviews the benefits and risks associated with various pharmacologic and psychological therapies to assess their ability to achieve the elimination of GAD symptomatology and restoration of normal function. Psychotherapeutic approaches such as applied relaxation, cognitive therapy, and cognitive-behavioral therapy have all been shown to be effective when used as monotherapies and may be beneficial when used adjunctively. Current effective pharmacotherapies for patients with GAD include anxiolytic benzodiazepines, buspirone, and antidepressants including venlafaxine and paroxetine. Benzodiazepines have long been used to treat anxiety and are particularly appropriate in short-term treatment situations; however, their adverse side-effect profile and their inability to treat depression commonly comorbid with GAD renders them less than ideal in many situations. Buspirone has demonstrated anxiolytic benefits but, like benzodiazepines, shows negligible antidepressant action. Antidepressants like paroxetine and venlafaxine are not only effective antidepressants but also effective anxiolytics, thus implying their special ability to treat GAD and concurrent depression, even over the long-term.

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Generalized anxiety disorder (GAD) did not become formally diagnosable until 1980 with the publication of the DSM-III. Current DSM-IV diagnostic criteria include excessive anxiety and worry occurring more days than not for at least 6 months, or trouble controlling excessive worry and anxiety, among others. Despite using different diagnostic criteria, 2 major epidemiologic surveys found comparable 1-year and lifetime prevalence rates in the United States. Data from the Epidemiologic Catchment Area (ECA) using DSM-III diagnostic criteria showed 1-year prevalence rates of 2.0% to 3.5% and lifetime prevalence rates of 4.1% to 6.6%. Data from the National Comorbidity Survey (NCS) using DSM-III-R criteria observed similar prevalence rates: 3.1% 1-year prevalence and 5.1% lifetime prevalence (Figure 1).[1] Despite indications of substantial prevalence, GAD often goes undiagnosed.[2] Patients diagnosed with the disorder tend to exhibit chronic functional impairment, seek general medical services at an elevated rate, and develop comorbid psychiatric disorders.[1]

Effective treatment should ultimately aim at the elimination of anxiety symptoms and the complete restoration of normal functioning. Although treatment may be complicated by the presence of other psychiatric disorders, achieving these treatment goals may decrease the rate of overutilization of medical services and the occurrence of other disorders, but research has yet to confirm this hypothesis. This article will review treatment options currently available to physicians treating GAD and preview potential future treatments. Current options include various kinds of psychotherapy and a battery of pharmacotherapy classes such as benzodiazepines, azapirones, and antidepressants, among others. This article will also examine how the use of diagnosis and treatment guidelines such as algorithms may facilitate implementation of treatment and the goal of eliminating symptoms and restoring functionality.
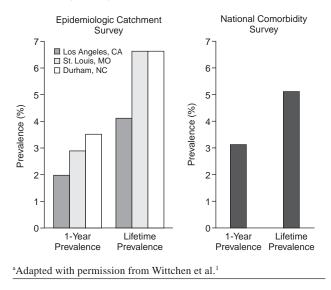
PSYCHOTHERAPY

Patients with GAD tend to have cognitive abnormalities that hinder their ability to effectively deal with symptoms associated with GAD and other aspects of their environment. For example, in patients with GAD, worry impedes the normal processing of information when attention, memory, or problem solving faculties are employed.[3] As a result, patients with GAD are more likely to incorrectly interpret external stimuli as dangerous or threatening,[4] regard unlikely events as likely,[5] or manifest these symptoms somatically through inordinate muscle tension. Psychotherapy is designed to help patients develop cognitive or behavioral strategies to effectively manage both cognitive and somatic symptoms that impede normal functionality.

Figure 1. 1-Year and Lifetime Prevalence Rates of GAD in the Epidemiologic Catchment Survey and National Comorbidity Survey[a]

[a]Adapted with permission from Wittchen et al.[1]

Early psychosocial therapies targeted the somatic manifestations of anxiety, such as increased physical tension, through relaxation techniques.[6] However, Borkovec and Whisman[7] concluded that cognitive-behavioral therapy (CBT) produced clinically and statistically significant benefits that were sustained for 6 to 12 months. They also found that using relaxation therapy in conjunction with cognitive therapy frequently reduced the need for medications and produced the greatest degree of benefit among compared psychotherapies. A review of studies by Fisher and Durham[8] found recovery rates at a 6-month follow-up between 50% and 60% among patients treated with CBT or applied relaxation. Using psychotherapy and pharmacotherapy in conjunction has shown potential as a treatment of depression,[9] so it is possible that a similar strategy may also be effective in the treatment of GAD.

PHARMACOTHERAPIES

In addition to psychotherapies, physicians have at their disposal numerous effective pharmacologic treatments. Recently developed drugs have been shown to be not only more effective than placebo, but also safer and more tolerable than the older medications such as benzodiazepines. Also, current research into the biological mechanisms of GAD is beginning to be converted into potential future therapies.

Benzodiazepines

Benzodiazepines have been used since the 1960s because of their anxiolytic, anticonvulsant, and muscle relaxant properties. Research has shown that the effects of benzodiazepines are mediated through an activation of the γ-aminobutyric acid (GABA) system at the $GABA_A$ receptor complex, which leads to reduced neural transmission throughout the central nervous system.[10] Benzodiazepines can be short-acting or long-acting, and both kinds have been shown to have a rapid onset of anxiolytic action in patients with GAD.[11,12] However, their role in long-term treatment of anxiety disorders is limited, given evidence that more than one third of those treated with benzodiazepines will not remit[13] and, some, but by no means all, studies have found that their effect does not differ significantly from placebo after the initial 4 to 6 weeks of treatment.[7,14]
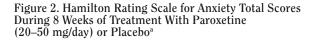
Failure of benzodiazepines to produce remission in a substantial number of patients renders their use difficult to recommend especially given modern commitments to the higher treatment standard of symptom elimination. In addition, benzodiazepines do not effectively ameliorate the principal cognitive symptom of GAD, namely worry, despite being able to positively impact the somatic manifestations of anxiety.[11,15,16] Also, benzodiazepines fail to reduce depressive symptoms and in some cases even exacerbate them,[17] an especially pressing limitation given the high rate at which GAD and depression occur comorbidly.
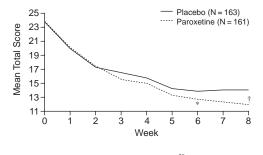
Benzodiazepines have also been associated with adverse cognitive side effects such as sedation, hypnotic effects, and motor impairment.[12] Abuse among those treated with benzodiazepines is uncommon[10] and patients treated with benzodiazepines over an extended period of time rarely increase the dose due to diminished efficacy.[18] However, the potential exists for patients to develop a physical dependence on benzodiazepines and withdrawal symptoms upon discontinuation, especially if the discontinuation is abrupt.[12]

Buspirone

The azapirone class of medications, which includes buspirone, is pharmacologically and structurally distinct from the benzodiazepines, but, like the benzodiazepines, possesses anxiolytic properties. Although the mechanisms of action of the azapirones are incompletely understood, it has been hypothesized that they function through a reduction of the firing of serotonin-affected nerve fibers by means of presynaptic serotonin agonism.[19]

Among patients with GAD, buspirone has been associated with reductions in levels of anxiety comparable to reductions associated with benzodiazepines.[20–24] Despite comparable efficacy, buspirone tends to have a slower onset of action than benzodiazepines, often taking 2 weeks or more to manifest efficacy.[20–24] Buspirone, unlike benzodiazepines, affects the cognitive aspects of GAD[15] but does not impair cognitive or psychomotor function or induce sedation, muscle relaxation, or withdrawal syndrome.[17,19] However, buspirone has been associated with adverse effects such as dizziness, headache, and nausea.[19] Also, due to a relatively short plasma half-life, buspirone requires regular dosing, which tends to result in poor treat-

Figure 2. Hamilton Rating Scale for Anxiety Total Scores During 8 Weeks of Treatment With Paroxetine (20–50 mg/day) or Placebo[a]

[a]Reprinted with permission from Pollack et al.[30]
*p = .05. †p < .01.

Figure 3. Hamilton Rating Scale for Anxiety (HAM-A) Psychic Cluster Scores at Baseline and During 8 Weeks of Treatment With Imipramine (50–100 mg/day), Paroxetine (20 mg/day), or 2′-Chlordesmethyldiazepam (3–6 mg/day)[a]

[a]Adapted with permission from Rocca et al.[26]
*p < .05 paroxetine and imipramine vs. 2′-chlordesmethyldiazepam.

ment compliance and difficulties sustaining appropriate levels of medication, thus pragmatically mitigating the drug's anxiolytic efficacy.[25] Finally, the use of buspirone as a treatment of GAD may be complicated by both its lack of antidepressant effects and the high rate of comorbid depression among patients with GAD.[1]
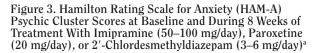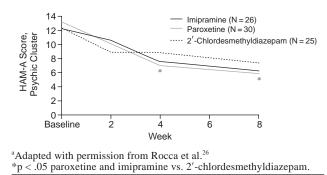
ANTIDEPRESSANTS

Tricyclic Antidepressants

Controlled studies of the use of tricyclic antidepressants (TCAs) to treat GAD have produced data demonstrating their efficacy.[11,16,26] For example, imipramine has been shown to be as effective an anxiolytic as benzodiazepines in the treatment of GAD, but like buspirone, exhibits greater benefit to the cognitive dimensions of the disorder than to somatic symptoms.[11,16,26] In addition to its anxiolytic function, imipramine has antidepressant effects that prove important in light of the high coincidence rate of GAD and depression.

Imipramine, like most TCAs, functions as an anxiolytic and an antidepressant by inhibiting both serotonin and norepinephrine reuptake throughout the central nervous system. However, the action of TCAs including imipramine is not limited to these mechanisms and has been found to include additional pharmacologic effects such as blocking certain histamine, epinephrine, and muscarinic receptors. These additional pharmacologic effects may contribute to the adverse effect profile of TCAs,[27] which includes postural hypotension, edema, blurred vision, and constipation.[28] Perhaps of gravest concern is the toxicity and even lethality of TCAs in overdose situations. Consequently, the use of TCAs to treat GAD may be complicated by their adverse side effect profile.

Selective Serotonin Reuptake Inhibitors

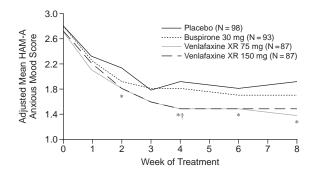Selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective treatments of both depressive and anxiety disorders such as obsessive-compulsive disorder (OCD), panic disorder, and social phobia.[29] Although multiple SSRIs might demonstrate efficacy as treatments for GAD, currently paroxetine is the only SSRI approved for such use by the U.S. Food and Drug Administration.

In a study of 161 people treated with 20 to 50 mg/day of paroxetine compared with 163 treated with placebo, paroxetine was associated with significant decreases in anxiety symptoms as manifested by reductions in mean total score on the Hamilton Rating Scale for Anxiety (HAM-A) (Figure 2).[30] Another study of the efficacy of paroxetine in treating anxiety[26] showed that, although paroxetine had a slower onset of action than a benzodiazepine, reductions of anxiety in those treated with paroxetine were significantly greater than in those treated with a benzodiazepine (Figure 3). Paroxetine, like buspirone, affects the psychic aspects of anxiety symptoms, and was shown by Pollack et al.[30] to induce remission in 43% of patients that completed the study and significantly improve social functioning. A longer-term study[31] of paroxetine in GAD has also been reported. In this 32-week mulitcenter study, patients were first treated single-blind for 8 weeks with flexible dose paroxetine and then randomized to receive continued active drug or placebo for an additional 6 months. The paroxetine group had a significantly lower relapse rate than the placebo group (10.9% versus 39.9%) and the time to relapse was also 4.7 times longer for the paroxetine than the placebo-treated patients. The proportion of patients achieving remission at the end of the single-blind phase was 43%; this increased to 73% by the end of the double-blind phase, compared with only 34% in the placebo group. Paroxetine was well-tolerated in this study.[31]

SSRIs tend to be safe and well-tolerated medications with only mild adverse side effects such as nausea, sleep disturbance, and sexual dysfunction. Given the ability of paroxetine to treat anxiety and depression that are often comorbid with GAD, paroxetine and perhaps other SSRIs

Figure 4. Hamilton Rating Scale for Anxiety Anxious Mood Item Scores (adjusted mean) at Baseline and During 8 Weeks of Treatment With Placebo, Buspirone 30 mg/day, or Venlafaxine 75 or 150 mg/day[a]

[a]Adapted with permission from Davidson et al.[35]
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.
*p < .05 venlafaxine 75 mg/day and 150 mg/day vs. placebo.
†p < .05 venlafaxine 75 mg/day and 150 mg/day vs. buspirone.

can play an important role in eliminating anxiety symptoms and meeting higher standards of treatment success for GAD.

Venlafaxine

Because neurobiological evidence implicates both the serotonin and norepinephrine systems in depressive and anxiety disorders,[32] it has been hypothesized that a medication modulating these systems would be an effective treatment of these disorders. Venlafaxine, which affects both neurochemical systems, was the first drug approved for the treatment of GAD and also has been shown to be effective in treating depression.[33,34]

In an 8-week study of the efficacy of the extended release (XR) formulation of venlafaxine (administered in 75-mg and 150-mg daily doses) compared with buspirone and placebo, venlafaxine was associated with significantly greater reductions on the anxious mood item of the HAM-A than both buspirone and placebo (Figure 4).[35] Katz et al.[36] pooled data from 5 placebo-controlled trials of venlafaxine for GAD. They found overall response rates of venlafaxine vs. placebo of 67% vs. 44%, respectively, in younger adults (p < .001) and 66% vs. 41% in older adults (p < .01).[36] Adverse effects associated with venlafaxine are generally mild and include dizziness, nausea, sexual dysfunction, and dry mouth, and most adverse effects substantially decrease during long-term treatment with the drug.[34] There is also a small risk of hypertension from venlafaxine.

In addition to the observed therapeutic benefits of venlafaxine over periods of 8 weeks and shorter, the agent has also been associated with long-term efficacy. In a 24-week investigation of venlafaxine XR, Allgulander et al.[37] found that it produced dose-dependent, significant reductions in HAM-A total scores. These data were corroborated by a flexible-dose study that showed significantly greater improvement for venlafaxine over placebo starting at week 1 or 2 and continuing for 27 more weeks.[38] Using a ≥ 50% reduction in baseline HAM-A scores as a criterion for response, Meoni and Hackett[39] found that 66% of patients receiving venlafaxine responded, while only 39% of those receiving placebo met the criterion for response. In addition, 43% of patients receiving venlafaxine satisfied the criterion for remission (HAM-A total score ≤ 7) compared with 19% of those receiving placebo.[39]

In addition to its antidepressive efficacy and long- and short-term anxiolytic efficacy, venlafaxine has been reported to improve social functioning[40]; however, more research is needed to confirm these reports. Taken together, these data suggest that venlafaxine can play a role not only in treating patients with depression but also in treating GAD. Moreover, the benefits of venlafaxine make it a valuable tool that may be used to reduce symptoms to subsyndromal levels or eliminate them entirely.

Potential Other Pharmacologic Treatments

The benefits offered by venlafaxine and paroxetine suggest that other antidepressants may possess anxiolytic properties. For example, an at least moderate improvement in anxiety was noted in 69% of patients treated with trazodone during an 8-week study of its anxiolytic effects.[11] Although the anxiolytic benefits were comparable to those of diazepam, adverse anticholinergic reactions were observed throughout the study. Nefazodone has also been associated with benefits among those with GAD[41] and those with comorbid anxiety and depression.[42,43] However, a commitment to the elimination of symptoms requires that long-term studies be conducted to examine the potential long-term therapeutic value of these drugs.

Atypical antipsychotics have also been proposed as a treatment for anxiety disorders such as GAD. These proposals are primarily derived from anecdotal evidence, case reports, and evidence of their ability to affect serotonin neurotransmission; however, controlled clinical trials are needed to investigate this hypothesis.

Others have speculated that some newer anticonvulsants may have anxiolytic properties based on neurobiological evidence that they affect the GABA system, a system also affected by benzodiazepines. Although no controlled studies of the anxiolytic uses of medications like tiagabine have confirmed this hypothesis, models of anxious behavior in rats[44] and case reports[45] suggest the possibility of therapeutic efficacy.

Various other potential medications have been proposed as treatments of GAD, but evidence of their potential efficacy has been mixed. Advances in neurobiology are identifying molecular entities, such as corticotropin-releasing factor antagonists and substance P receptor (neurokinin NK_1) antagonists, that may become targets of future medications.

CLINICAL IMPLICATIONS

Because patients with GAD often exhibit comorbid depression,[1] it is important for clinicians to have at least general treatment guidelines to apply.

In treating patients with GAD, physicians should first determine whether the patient would benefit more from pharmacotherapy, psychotherapy, or a combination of the 2. If pharmacotherapy is determined to be the most appropriate treatment, antidepressants with demonstrated anxiolytic effects such as venlafaxine XR and paroxetine should be used. The efficacy of these medications may be augmented by cognitive, cognitive-behavioral, and relaxation therapies. If psychotherapy is used first but does not produce treatment response, then pharmacotherapy may be added. However, in those cases in which patients do not respond to initial therapy or for other reasons require immediate relief of anxiety, benzodiazepines may be a suitable option due to their demonstrated rapid onset of action. If benzodiazepines are employed, they should be used in as small a dose and for as briefly as possible to maximize benefit and minimize the potential for adverse effects.

CONCLUSION

A knowledge of the overall benefits and risks associated with the available treatments of GAD and their commonly comorbid conditions leads to fairly clear guidelines for the treatment of GAD. Psychotherapies have been shown to be effective when used alone and may serve to augment the anxiolytic effects of pharmacotherapies. Although many medications currently available offer anxiolytic benefits, antidepressants are more effective than benzodiazepines and lack the treatment-disruptive effects of benzodiazepines. Benzodiazepines are still important tools, especially in severe or acute situations when more immediate anxiolytic effects are required, but antidepressants such as the 2 approved for GAD treatment, namely venlafaxine XR and paroxetine, should be considered the first line of pharmacotherapeutic options.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), chlordiazepoxide (Librium and others), diazepam (Valium and others), hydroxyzine (Atarax and others), imipramine (Tofranil and others), nefazodone (Serzone), paroxetine (Paxil), tiagabine (Gabatril), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, imipramine, nefazodone, tiagabine, and trazodone mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of generalized anxiety disorder.

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