Pharmacotherapy of Generalized Anxiety Disorder

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Benzodiazepines have traditionally been used to treat acute anxiety disorders, but they are not ideal in the treatment of chronic generalized anxiety disorder (GAD). Following long-term therapy, benzodiazepines have the potential to produce dependency and withdrawal symptoms. In addition, although agents such as the benzodiazepines and buspirone alleviate anxiety, they have little effect on depression, which is a common comorbidity of GAD. Antidepressants have long been viewed as promising alternatives to benzodiazepines for the treatment of some types of anxiety. Although they have been shown to be useful in the treatment of panic disorder, social anxiety disorder/social phobia, and obsessive-compulsive disorder, they have not until recently been regarded as potential therapies for GAD. Treatment with antidepressants has opened up a new area of investigation into the pharmacotherapy of GAD, with a growing body of evidence supporting the role of therapies such as paroxetine and venlafaxine extended release. *(J Clin Psychiatry 2001;62[suppl 11]:46–50)*

Generalized anxiety disorder (GAD) is a chronic and disabling disorder and is one of the most prevalent of the anxiety disorders, with an estimated lifetime prevalence of 5% to 6%.[1] Depression is commonly associated with GAD, and this comorbidity increases the severity and burden of the condition. However, the benzodiazepines and buspirone, which are effective in alleviating anxiety are not effective in the treatment of depression. This, coupled with the potential of benzodiazepines to produce dependency and withdrawal symptoms, has meant that in recent years there has been an increased interest in finding alternatives to the benzodiazepines for the treatment of GAD. Antidepressants have been used to treat anxiety disorders for a number of years. However, although they have been shown to be useful in the treatment of panic disorder,[2–4] posttraumatic stress disorder,[5,6] and obsessive-compulsive disorder (OCD),[7] they have not until recently been regarded as pharmacotherapies for GAD, despite 1 study that found efficacy for imipramine.[8] Selective serotonin reuptake inhibitors (SSRIs) are being increasingly recognized as effective across the spectrum of depressive and anxiety disorders.

The comorbidity of GAD and depression means that there is an advantage in treating GAD with a therapy that is also effective against comorbid conditions. The need to improve pharmacotherapy for GAD is of particular importance in primary care, where the syndrome is present more often than it is recognized.[9] This article examines the pharmacologic treatment options that are available for GAD and reviews clinical data regarding the use of antidepressants in GAD.

TREATMENT GOALS OF PHARMACOTHERAPY FOR GAD

The main goal of pharmacotherapy in GAD is treatment of the core symptoms, including chronic worry, muscular tension, autonomic hyperactivity, and insomnia.[10] In addition to acute treatment (less than 6 months), patients with GAD frequently require chronic treatment (more than 6 months) to prevent relapse. Since medication may be continued over several months or even years, maintenance of long-term efficacy is essential. The possibility of long-term usage means that therapies are needed that are well tolerated and have minimal potential for abuse, dependency, or withdrawal problems. Pharmacotherapies for GAD should have a rapid onset of action and demonstrate efficacy in comorbidity and the reduction of disability while improving patient quality of life.

PHARMACOLOGIC TREATMENT OPTIONS FOR GAD

The literature refers to a number of studies in the treatment of GAD. However, many of these (including those with the older benzodiazepines) are based on DSM-III criteria. The treatment options for which controlled data in GAD are available are benzodiazepines, serotonin-1A (5-HT_{1A}) partial agonists, antidepressants, and hydroxyzine.

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Benzodiazepines

Although benzodiazepines have traditionally been used to treat acute anxiety disorders, they are in some ways less effective than antidepressants in the treatment of GAD (see the following sections). The efficacy and relative safety of benzodiazepines when prescribed for a few weeks are well established.[11,12] The main disadvantage of short-term therapy is sedation, to which tolerance frequently develops.[13] However, long-term usage has been associated with physical dependence and withdrawal symptoms, including dysphoria and convulsions, and side effects such as ataxia, sedation, and memory disturbance.[14] Moreover, long-term usage may lead to the development of major depression.[15] Some of the evidence supporting the use of benzodiazepines in the treatment of anxiety disorders has been questioned,[16] and thus alternative treatments have been sought.

5-HT$_{1A}$ Partial Agonists

As a group, the 5-HT$_{1A}$ partial agonists have proved to be disappointing in the treatment of GAD. The exception is the azapirone, buspirone, introduced in the United States in 1986.[17–19] Initial findings in patients with GAD generally showed that buspirone was as efficacious as the benzodiazepines in treating anxiety disorders,[20–23] but appeared to lack the same side effects and withdrawal symptoms.[24] Subsequently, some studies have reported conflicting results for buspirone,[25,26] while others demonstrate a gradual onset of action for this drug,[13,23,27] creating a need for the identification of alternative agents.

Antidepressant Agents

Tricyclic antidepressant agents. There is evidence that tricyclic antidepressants (TCAs) are at least as effective as benzodiazepines in the treatment of GAD,[28] and may be superior in long-term therapy, with particular efficacy in the reduction of psychic symptoms.[8,29,30] Although TCAs exhibit a range of pharmacologic effects, tertiary TCAs with both noradrenergic and serotonergic effects, such as imipramine and amitriptyline, appear to be consistently effective in the treatment of anxiety.[31]

In 1980, a 5-week, placebo-controlled study compared the efficacy of the TCA amitriptyline with the benzodiazepine diazepam in 240 outpatients with mixed anxiety neurosis and depressive neurosis.[28] The authors found that amitriptyline was as effective as diazepam in those patients suffering predominantly from either anxiety or depressive symptoms.

Two further studies in patients with GAD demonstrated an antianxiety effect for TCAs comparable to that of the benzodiazepines.[8,30] The first of these was a 6-week study that compared a relatively low dose of the TCA imipramine (91 mg/day; range, 25–200 mg/day) with the benzodiazepine alprazolam (2.2 mg/day; range, 0.5–6.0 mg/day) in 60 patients with GAD.[30] Low dropout rates were reported for both drugs in this study (13% and 6% for imipramine and alprazolam, respectively).

Considered overall, efficacy against a number of symptoms appeared to favor treatment with imipramine over alprazolam. Efficacy was demonstrated for state anxiety as measured by the State-Trait Anxiety Inventory (STAI)[32]; anxiety, obsessive-compulsive behavior, interpersonal sensitivity, depression, paranoia, and psychoticism as measured by the Hopkins Symptom Checklist-90 (HSCL-90)[33]; and contentment, hostility, guilt, and depression as measured by the Affects Balance Scale.[34] Somatic measures appeared to favor alprazolam; these included cardiopulmonary and sleep improvement on the Somatic Symptom Scale[35] and autonomic and cardiovascular symptoms on the Hamilton Rating Scale for Anxiety (HAM-A).[36] From these results, the authors concluded that alprazolam was more effective than imipramine in reducing somatic anxiety, but that imipramine was more effective in reducing psychic symptoms, including anticipatory thinking and dysphoria. The authors also concluded that patients who are chronic worriers, tend to fear interpersonal relationships, or have strong tendencies toward rumination respond better to antidepressants than to benzodiazepines. They recommended that the anxiolytic potential of other, better-tolerated antidepressants be investigated.

The other study[8] was placebo-controlled and compared imipramine (mean maximum daily dose = 143 mg) and trazodone (255 mg) with diazepam (26 mg) in 230 patients with GAD. All 3 active treatments were more effective than placebo in improving GAD, with the highest response rate being seen with imipramine (73% of patients compared with 69%, 66%, and 47% of patients for trazodone, diazepam, and placebo, respectively). Imipramine was found to be more effective than diazepam and placebo for psychic anxiety, whereas trazodone was more effective than placebo. Imipramine, trazodone, and diazepam were all more effective than placebo for somatic anxiety.

The results from these studies suggest that the psychic and somatic symptoms experienced by patients with GAD respond differently to pharmacologic intervention and that an antidepressant can work effectively on both domains.

Selective serotonin reuptake inhibitors. The efficacy of SSRIs has been demonstrated in placebo-controlled studies in anxiety disorders, including obsessive-compulsive disorder, panic disorder, and social phobia.[37–40] Only more recently has the efficacy of SSRIs in the treatment of GAD been investigated.

One of the initial studies was an 8-week comparison[41] of paroxetine (20 mg/day), imipramine (50–100 mg/day), and 2'-chlordesmethyldiazepam (3–6 mg/day) in 81 patients fulfilling the DSM-IV[42] criteria for GAD. From week 4 onward, both the paroxetine- and imipramine-treated patients showed a greater improvement on the HAM-A[36] than benzodiazepine-treated patients. The change from baseline in the HAM-A total score at week 8

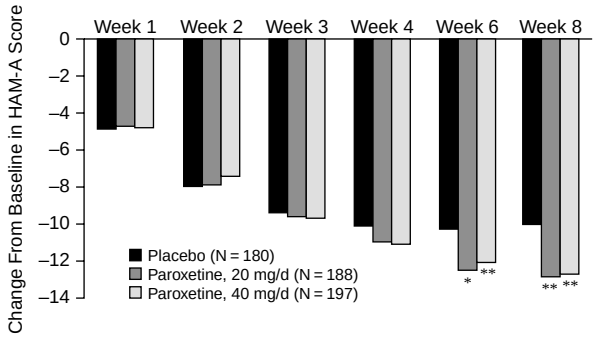
was 15.6 for paroxetine compared with 13.9 and 11.8 for imipramine and 2'-chlordesmethyldiazepam, respectively. Paroxetine demonstrated a statistically significant difference in improvement on the HAM-A compared with 2'-chlordesmethyldiazepam after 4 weeks of treatment ($p < .05$), while the results for imipramine differed significantly from the benzodiazepine only at week 8 ($p < .05$). Both imipramine and paroxetine preferentially improved psychic symptoms, while 2'-chlordesmethyldiazepam was more effective in the resolution of somatic symptoms.

As anticipated, in the study by Rocca et al.,[41] the percentages of patients experiencing the anticholinergic side effects of dry mouth and constipation were significantly greater in the imipramine group (56% and 39%, respectively) than with paroxetine (8% for both events) or 2'-chlordesmethyldiazepam (10% and 5%, respectively) ($p < .001$ for dry mouth, $p < .01$ for constipation). Significantly more 2'-chlordesmethyldiazepam–treated patients (60%) experienced drowsiness than imipramine- or paroxetine-treated patients (39% and 4%, respectively) ($p < .01$). Paroxetine was generally well tolerated with the exception of nausea, which was observed more frequently (40% of patients) than with the other treatments (6% of imipramine-treated patients and 5% of 2'-chlordesmethyldiazepam–treated patients). The dropout rates were similar for paroxetine (17%) and 2'-chlordesmethyldiazepam (20%), but the highest rate was reported with imipramine (31%). The results from this initial study demonstrate the efficacy of paroxetine relative to active control treatments in GAD. Subsequently, 3 placebo-controlled, 8-week studies[43,44] (2 in the United States and 1 in Europe) further evaluated paroxetine in the treatment of GAD.

A large multicenter, fixed-dose study[43] conducted in the United States compared the efficacy of paroxetine, 20 and 40 mg/day, in 566 patients with GAD.[43] Dosing began at 10 mg/day. At week 8, both doses of paroxetine showed a statistically significant reduction from baseline on the HAM-A total score compared with placebo ($p < .001$) (Figure 1). This finding was further substantiated by the changes noted in Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. There was an improvement in disability in paroxetine-treated patients, as shown on the patient self-rated Sheehan Disability Scale score. At week 8, there was a statistically significant reduction from baseline for both paroxetine doses compared with placebo ($p < .001$). The mean changes from baseline at week 8 were –6.1, –6.6, and –3 for paroxetine, 20 mg/day; paroxetine, 40 mg/day; and placebo, respectively. Based on these findings, the authors concluded that paroxetine is an effective treatment for patients with GAD.

The other 2 studies were flexible-dose studies using paroxetine, 20 to 50 mg/day.[44] The first study (Study 642) was conducted in the United States and used an initial dose of 10 mg/day, whereas the second study (Study 637) was conducted in Europe and used a starting dose of 20 mg/day. Study 642 demonstrated a statistically significant improvement in paroxetine-treated patients over placebo as measured by mean reduction in HAM-A score at weeks 6 and 8 ($p = .041$ and $p = .008$, respectively). In Study 637, there was a statistically significant reduction in HAM-A score for paroxetine compared with placebo in the intent-to-treat observed-case dataset ($p < .05$).

Figure 1. Change From Baseline in Hamilton Rating Scale for Anxiety (HAM-A) Score for Paroxetine, 20 mg/day; Paroxetine, 40 mg/day; and Placebo in an 8-Week, Fixed-Dose Study[a]



[a]Data from Bellew et al.[43] Changes shown for intent-to-treat population. Difference from placebo in mean change at week-8 endpoint = –2.9 for paroxetine, 20 mg/day; –2.6 for paroxetine, 40 mg/day.
*$p = .002$.
**$p < .001$.

In all 3 studies, the percentage of responders (50% reduction from baseline in HAM-A total score) at week 8 was greater with paroxetine than with placebo. In the fixed-dose study, 55% and 60% of patients receiving paroxetine, 20 mg/day and 40 mg/day, respectively, responded to treatment compared with 40% of patients in the placebo group ($p = .007$ and $p < .001$, respectively). In Study 637, the response rates were 57.0% for paroxetine and 49.7% for placebo, whereas in Study 642, the response rates were 63.8% and 43.6%, respectively.

There were no significant differences between the side effect profiles reported for paroxetine and placebo across the 3 studies, nor were there differences in tolerability.

Serotonin-norepinephrine reuptake inhibitors. Venlafaxine extended release (XR) is a serotonin-norepinephrine reuptake inhibitor (SNRI). Venlafaxine XR has been reported to alleviate anxiety in patients with depression.[45] Two placebo-controlled studies[46,47] have demonstrated the efficacy of venlafaxine XR in GAD and have provided evidence that both the psychic and somatic manifestations of anxiety can be controlled.

The first of these studies[46] compared the efficacy of 2 fixed doses of venlafaxine XR (75 mg/day and 150 mg/day) with 30 mg/day of buspirone over an 8-week treatment period in 365 patients with GAD. The mean adjusted HAM-A anxious mood and tension scores were sig-

nificantly lower for both doses of venlafaxine XR at week 8 compared with placebo ($p < .05$). However, the adjusted mean total HAM-A scores for all the treatment groups compared with placebo were not significant (13.0, 13.8, and 15.6 for venlafaxine XR 75 mg/day and 150 mg/day and placebo, respectively). A significantly higher response rate as measured on the CGI was seen for venlafaxine XR, 75 mg/day, compared with buspirone at weeks 3, 4, and 8, and with placebo at all timepoints after week 1 ($p < .05$). The CGI response rates at week 8 were 62%, 49%, 55%, and 39% for venlafaxine XR, 75 mg/day; venlafaxine XR, 150 mg/day; buspirone; and placebo, respectively.

Both doses of venlafaxine XR produced statistically significant improvements on the Hospital Anxiety and Depression (HAD)[48] scale anxiety subscale compared with buspirone (all timepoints except week 1; $p < .05$) and placebo (all timepoints except weeks 1 [both dosages] and 2 [difference found with 75 mg/day only]; $p < .05$) (Figure 2).

The second study[47] expanded the results of the above study[46] and another 8-week study[49] and evaluated flexible doses of venlafaxine XR over 6 months. The results from this study showed that the efficacy of venlafaxine XR, 75 to 225 mg/day, could be sustained in 238 patients with GAD over a 28-week maintenance period. Venlafaxine XR was statistically superior to placebo at all timepoints as assessed on the HAM-A anxiety subscale ($p < .001$). The results from these 2 studies demonstrate the efficacy of venlafaxine XR in both the short- and long-term treatment of GAD, although the optimal dose was not defined.

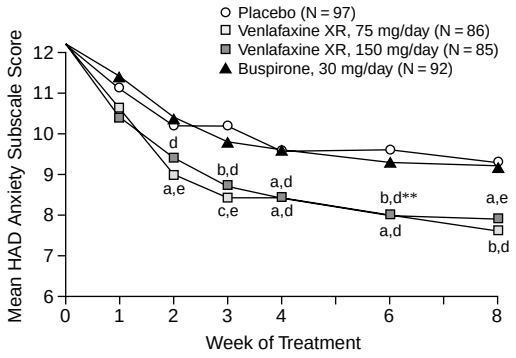
Miscellaneous Agents

Hydroxyzine. Hydroxyzine blocks both histamine-1 receptors and muscarinic receptors and has been marketed since 1955. Although hydroxyzine is unlikely to be used as first-line therapy for GAD, a recent placebo-controlled comparison with buspirone may provide some mechanistic information about the treatment of GAD.[50] Changes in HAM-A score from baseline to day 28 showed a significant difference between hydroxyzine and placebo ($p < .02$), but not between buspirone and placebo. The endpoint changes were 10.8, 8.8, and 7.2 for hydroxyzine, buspirone, and placebo, respectively.

HEART RATE VARIABILITY

Heart rate variability (HRV) is decreased in GAD and during worry.[51] However, there is evidence that treatments for GAD and panic disorder, whether psychosocial or pharmacologic, help to increase heart rate variability. HRV in GAD is increased by cognitive-behavioral therapy,[51] while paroxetine increases HRV in panic disorder.[52] In view of these findings, these therapies might have the potential to restore a degree of flexibility and adaptability at a physiologic level in patients. Imipramine, however, decreases HRV in panic disorder.[53]

Figure 2. Mean Hospital Anxiety and Depression (HAD) Scale Anxiety Subscale Scores for Venlafaxine XR, 75 mg/day; Venlafaxine XR, 150 mg/day; Buspirone, 30 mg/day; and Placebo in an 8-Week Study*



*Reprinted, with permission, from Davidson et al.[46] Abbreviation: XR = extended release.
**150-mg/day group.
[a]$p < .05$ vs. placebo.
[b]$p \leq .005$ vs. placebo.
[c]$p < .001$ vs. placebo.
[d]$p \leq .05$ vs. buspirone.
[e]$p \leq .01$ vs. buspirone.

CONCLUSION

Clinical studies have shown that antidepressants are as effective in the treatment of GAD as they are for other anxiety disorders. In general, they are preferable to benzodiazepines and buspirone, especially when comorbidity and/or psychotic anxiety, including depression, is present. TCAs appear to be at least equivalent, and may be superior to, the benzodiazepines in the short term and remain effective in the long term.[8,30] However, side effects, especially anticholinergic events, limit the use of TCAs in many patients, especially the elderly or those with cardiovascular disease. The antianxiety effects of paroxetine compare well with those of imipramine.

SSRI or SNRI antidepressant therapy can facilitate treatment in pure GAD, pure depression, and mixed states when a primary diagnosis of either anxiety or depression is difficult to establish. Since there is frequent comorbidity of depression and anxiety, the use of such antidepressant therapy in patients with a comorbid diagnosis may be of significant value. Recent data, therefore, suggest that antidepressants are first-line therapy for GAD.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), buspirone (BuSpar), diazepam (Valium and others), paroxetine (Paxil), venlafaxine (Effexor).

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