Treatment of Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is characterized by chronic worry that may persist for many years. It is a debilitating disorder, and effective long-term treatment is required. Psychotherapy, particularly relaxation, cognitive therapy, and cognitive-behavioral therapy, has shown long-term benefit in GAD and may be a useful approach alone and as an adjunct to pharmacotherapeutic options. Available medications for GAD include benzodiazepine anxiolytics, buspirone, and antidepressants. Although benzodiazepines are effective as short-term anxiolytics, their use is compromised by a poor adverse event profile and, like buspirone, they lack the antidepressant efficacy important for addressing the comorbid depression experienced by many patients with GAD. Antidepressants, including paroxetine and the serotonin-norepinephrine reuptake inhibitor venlafaxine, are effective anxiolytics and resolve symptoms of depression in patients with GAD. The benefit of venlafaxine is sustained long term, enabling increased numbers of patients to attain remission from symptoms and experience restoration of normal functioning. Although further clinical studies are required to establish the use of psychosocial therapy in the treatment of GAD, preliminary results are encouraging. At present, the use of psychosocial therapy and second-generation antidepressants, such as some selective serotonin reuptake inhibitors and venlafaxine, offer the best approach to attaining long-term benefit for patients with GAD.
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Generalized anxiety disorder (GAD) was created as a distinct diagnostic entity in 1980 (DSM-III)[1] and is characterized by excessive worry about multiple life circumstances. Patients with this disorder present as chronically anxious individuals who experience marked impairment of daily functioning.[2,3] Frequently, patients have suffered from GAD for their entire lives and are thus inured to their symptoms. They may not seek treatment until additional psychiatric illnesses have developed, including depression, substance abuse, and other anxiety disorders. The presence of these additional disorders may then obscure the underlying diagnosis of GAD, which could explain, in part, both the skepticism of some psychiatrists regarding the existence of GAD as a distinct diagnosis and the underrecognition of this disorder,[4] probably contributing to the reported undertreatment of GAD[5] and the poor long-term outcome.[6] However, the need for effective treatment is recognized, not only to attain reduction in symptoms, but to attain remission and restore patients to normal functioning, an approach that may necessitate long-term therapy.[7] This article will therefore review the available options for the treatment of GAD, including the use of psychotherapy or drug treatment with benzodiazepines, azapirones, or antidepressants, and consider the best approaches to the resolution of this disorder.

PSYCHOTHERAPY

Psychotherapy aims to help patients develop effective strategies to cope with symptoms of anxiety. Evidence has been reported to suggest the presence of cognitive abnormalities in patients with GAD. For example, patients display selective attentional biases when presented with threat-related information[8] and have an explicit memory bias for threat words.[9] The perception of uncontrollability or danger in worry, and negative appraisal of worrying, may also maintain the pathology of GAD.[10] Addressing this unrealistic outlook by cognitive therapy and cognitive-behavioral therapy (CBT) has therefore been effective for patients with GAD.[11–14] Studies have shown recovery rates at 6-month follow-up of 51% in patients receiving CBT.[11] It also appears that relapse rates following this therapy are low.[14] By targeting the intolerance of uncertainty during CBT, patients experience a statistically and clinically significant improvement in symptoms, which is sustained at 6- and 12-month follow-up.[15] Applied relaxation to target

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the excessive worry and muscle tension of GAD is also an effective treatment.[11,13,14] A recovery rate of 60% has been reported,[11] with the size of effect for applied relaxation being greater than for cognitive therapy or CBT.[13] In contrast, analytical psychotherapy appears to offer no benefit to patients with GAD, the recovery rate being only 4% at 6-month follow-up.[11] A combination of psychotherapy and pharmacotherapy is promising for the treatment of depression,[16] and so it is possible that a similar combined approach may prove efficacious in the treatment of GAD.

BENZODIAZEPINES

Benzodiazepines became widely available in the 1960s. They all have anxiolytic, hypnotic, anticonvulsant, and muscle relaxant properties, which are mediated by potentiating the effects of gamma-aminobutyric acid (GABA) at $GABA_A$ receptors/chloride ion channel complexes. This interaction leads to hyperpolarization and reduced neural transmission throughout the central nervous system.[17] The anxiolytic efficacy of individual benzodiazepines is similar across the group, and agents are distinguished by their pharmacokinetic properties, being either long-acting (diazepam, clonazepam, chlordiazepoxide), due to hepatic cytochrome P450–mediated generation of active metabolites, or short-acting (alprazolam, oxazepam, lorazepam).[17] Benzodiazepines are anxiolytic in patients with GAD and have a rapid onset of action.[18–22] However, their efficacy in long-term treatment may not be as robust as assumed. For example, of patients responding to treatment, less than two thirds will remit[23] and a number of studies have indicated that, despite early improvement in anxiety symptoms, the effects of benzodiazepines are not significantly different from placebo after 4 to 6 weeks' treatment.[21,24–26] Moreover, the benefit of benzodiazepines extends primarily to relief of somatic symptoms, rather than the psychological symptoms that include worry, a key feature of GAD.[21,27–30] In addition, benzodiazepines do not improve symptoms of depression and may actually enhance these symptoms,[31] which presents a significant drawback in light of the high incidence of comorbid GAD and depression.[2]

The use of benzodiazepines is associated with a number of adverse events, including sedation, motor impairment, and cognitive impairment.[17,22] They have thus been linked as a cause of automobile accidents through impaired driving skills, with the generation of persistent cognitive impairment, and with an increased risk of falls in the elderly.[17,32–34] Although risks of tolerance and abuse have been linked to benzodiazepines, patients taking these agents over extended periods do not increase their dose over time[35] and, with the exception of individuals with preexisting substance abuse, the abuse of benzodiazepines is rare.[17] However, they do have the potential for generating physical dependence and withdrawal reactions when discontinued. This syndrome, which may occur when withdrawing after only 2 weeks' treatment with benzodiazepines,[36] is characterized by rebound anxiety, agitation, insomnia, and sensory disturbances[17] and is worse with longer administration, high dose, and abrupt discontinuation.[22] Hence, it is always recommended to gradually taper benzodiazepines when attempting to discontinue them.[37]

AZAPIRONES

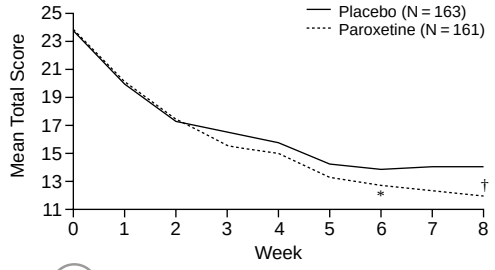
The azapirone group of compounds, which includes buspirone, ipsapirone, and gepirone, is structurally and pharmacologically unrelated to benzodiazepines, but also has anxiolytic properties.[19,20,25,27,38] The mechanism of the anxiolytic action of buspirone and other azapirones is not fully understood, but has been speculated to involve reduced firing of serotonergic nerve fibers through the partial agonist effect of these compounds at presynaptic serotonin-1A ($5\text{-}HT_{1A}$) autoreceptors on serotonergic nerve cell bodies.[39] Buspirone reduces anxiety in patients with GAD to an extent comparable to that attained with benzodiazepines, although this effect of buspirone is slower in onset, taking at least 2 weeks to become evident.[40–47] Ipsapirone and gepirone are similarly effective in GAD,[48–51] although buspirone is the only agent currently available from this group. Unlike benzodiazepines, buspirone appears to exert benefit primarily on psychic symptoms of anxiety[27] and does not interact with other central nervous system depressants or produce cognitive impairment, psychomotor adverse events, muscle relaxation, or a withdrawal syndrome on discontinuation.[17,39] The adverse effects of buspirone are generally mild and include dizziness, headache, and nausea.[39] Some reports have suggested that the effects of azapirones are not dose-related[46,49] or are only modest in comparison to placebo.[52,53] This may reflect study design, since the short plasma half-life of buspirone necessitates regular dosing, often 3 times daily, leading to poor compliance and receiving suboptimal dosages, thus reducing efficacy.[54] Further observations made during the use of buspirone indicate that it may be ineffective in patients who have previously responded to treatment with benzodiazepines[55]; furthermore, buspirone lacks antidepressant effects. These factors may have implications in the treatment of GAD, given the prior use of benzodiazepines by patients[56] and the incidence of comorbid depression.[2]

ANTIDEPRESSANTS

Tricyclic Antidepressants

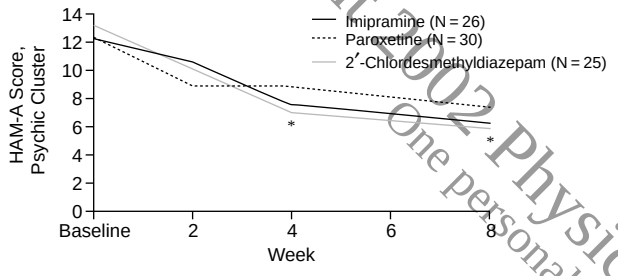
Analyses of data obtained in patients with anxiety neurosis have suggested that tricyclic antidepressants (TCAs) are effective in relieving patients' symptoms.[38,57] Efficacy of TCAs in the treatment of GAD has subsequently been confirmed in controlled studies.[21,28,30] The anxiolytic effect of imipramine is equivalent to or greater than that attained by benzodiazepines, although it is slower in onset and more

Figure 1. 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.[64]
*p = .05. †p < .01.

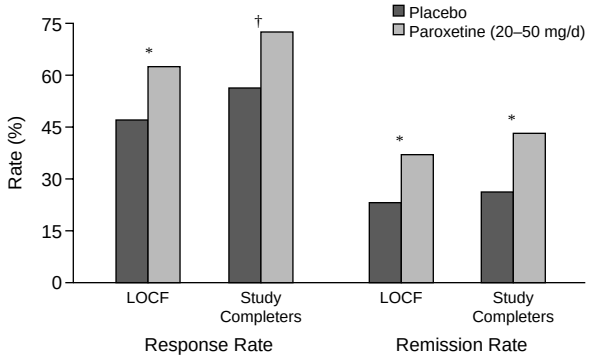
Figure 2. Hamilton Rating Scale for Anxiety (HAM-A) Psychic Cluster Scores at Baseline and During 8 Weeks of Treatment With Imipramine (50–100 mg/day), Paroxetine (20 mg/day), or 2′-Chlordesmethyldiazepam (3–6 mg/day)[a]



[a]From Rocca et al.[30]
*p < .05 paroxetine and imipramine vs. 2′-chlordesmethyldiazepam.

pronounced on the psychic, rather than somatic, symptoms of GAD.[21,28,30] Thus, imipramine provides a sustained reduction in symptoms of anxiety and, additionally, is efficacious in treating symptoms of depression. The anxiolytic and antidepressant effects of imipramine are mediated by inhibition of norepinephrine and serotonin reuptake in the central nervous system. However, TCAs, including imipramine, have additional pharmacologic effects such as blocking histamine H_1 receptors, α_1-adrenoceptors, and muscarinic receptors, which may underlie the adverse event profile of these agents.[58] Adverse events associated with TCAs include postural hypotension, edema, dry mouth, blurred vision, constipation, and weight gain. TCAs may interact with other drugs and can cause cardiac rhythm disturbances.[59] These adverse events do not wane over time, and in patients with panic disorder, enhancement of some symptoms of anxiety such as restlessness has been reported.[60] Of particular concern is the potential for toxic or lethal overdose with relatively small supplies of TCAs, and hence caution may be required in prescribing to patients with comorbid depression and suicidal thoughts.[61] The poor adverse event profile may therefore limit the use of these agents for the chronic treatment of GAD.

Figure 3. Response and Remission Rates for Patients Treated With Paroxetine (20–50 mg/day) or Receiving Placebo for the Last-Observation-Carried-Forward (LOCF) Group and for Those Patients Completing 8 Weeks of Treatment[a]

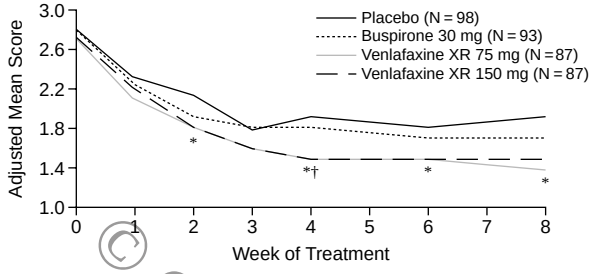


[a]Based on data from Pollack et al.[64] Response was defined as a score of 1 or 2 on the Clinical Global Impressions scale, and remission was defined as a score ≤ 7 on the Hamilton Rating Scale for Anxiety.
*p < .01. †p = .005.

Selective Serotonin Reuptake Inhibitors

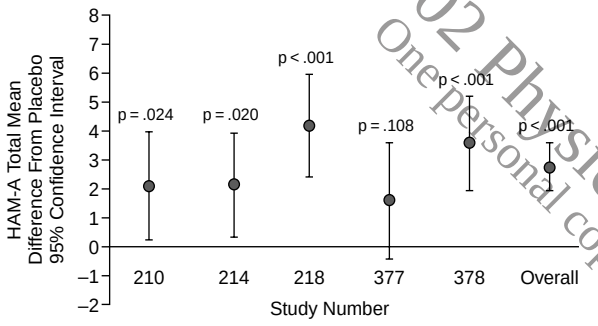
Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of depression and anxiety disorders, including obsessive-compulsive disorder (OCD), panic disorder, and social phobia.[62,63] The use of these agents in GAD has primarily been investigated with paroxetine. Compared with placebo, paroxetine at 20 to 50 mg/day was associated with an improvement in symptoms of anxiety (Figure 1).[64] In a separate study, the extent of this improvement was similar to that attained with imipramine.[30] In comparison with a benzodiazepine, the onset of action of paroxetine was slower, but the reduction in anxiety symptoms was significantly greater after 4 weeks' treatment (Figure 2).[30] Paroxetine was associated with an improvement in psychic symptoms of anxiety, and a reduction in the score of the anxious mood item of the Hamilton Rating Scale for Anxiety (HAM-A) was evident as early as 1 week after commencing treatment.[30,64] During up to 8 weeks' treatment with paroxetine, a significantly greater number of patients responded or remitted, compared with those receiving placebo (Figure 3).[64] Of those patients completing 8 weeks' treatment, 72% achieved a response and 43% achieved remission. Relatively high placebo response (56%) and remission (26%) rates, compared with similar studies, were also achieved.[64] Paroxetine administration was also associated with improvements in social functioning.[64] This result is consistent with other reports that patients with GAD show improved harm avoidance, cooperation, self-confidence, and responsibility following treatment with this agent.[65] SSRIs are generally safe and well tolerated, and the adverse events associated with administration are usually mild, including sleep disturbance, nausea, and sexual dysfunction. The long-term efficacy of paroxetine and 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]



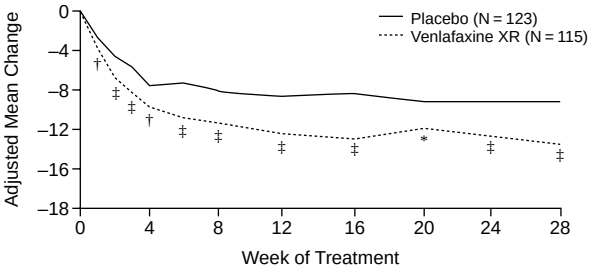
[a]Adapted with permission from Davidson et al.[53]
*p < .05 venlafaxine 75 mg/day and 150 mg/day vs. placebo.
†p < .05 venlafaxine 75 mg/day and 150 mg/day vs. buspirone.

Figure 5. Effect Size for the 8-Week Data From the 5 Placebo-Controlled Studies of Venlafaxine XR in Patients With Generalized Anxiety Disorder[a]



[a]Data on file, Wyeth Pharmaceuticals, Philadelphia, Pa.
Abbreviation: XR = extended release. These results demonstrate a clinically significant effect size with venlafaxine XR that is similar in all 5 studies. Combining the data from all studies shows a highly significant anxiolytic effect of venlafaxine.

Figure 6. Results From a Long-Term Flexible-Dose Study in Patients With Generalized Anxiety Disorder[a]



[a]Reprinted with permission from Gelenberg et al.[74] Venlafaxine (mean daily dose = 176 mg) produces a significant anxiolytic response (change in Hamilton Rating Scale for Anxiety total score), compared with placebo, as early as 1 week into treatment that is sustained for 6 months.
*p < .01, †p < .005, ‡p < .001 venlafaxine XR vs. placebo.

beyond 8 weeks' treatment remains to be determined in patients with GAD, although paroxetine is the second agent to be indicated for the treatment of this disorder.

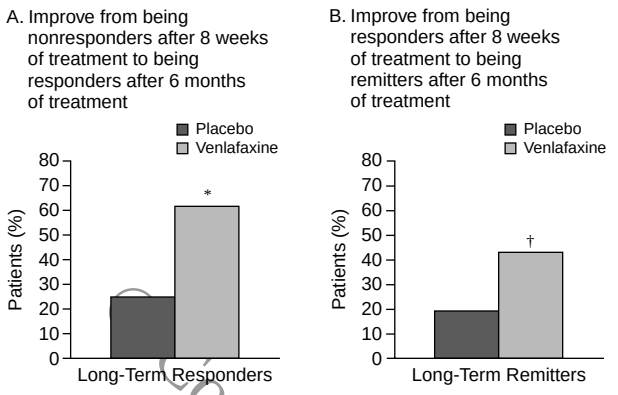
Serotonin-Norepinephrine Reuptake Inhibitor—Venlafaxine

Strong evidence exists that implicates pivotal roles for both the serotonin and norepinephrine systems in the neurobiology of anxiety and depression.[66] This evidence would therefore suggest that a serotonin-norepinephrine reuptake inhibitor (SNRI) might be effective in the treatment of these disorders. Indeed, venlafaxine has been shown to be effective in the treatment of depression and GAD[67,68] and is the first agent indicated for the long-term treatment of GAD.

In one study, administration of venlafaxine (75–225 mg/day) for 8 weeks resulted in a reduction in HAM-A total score that was significantly greater than that attained by placebo or buspirone (Figure 4)[53] and was associated with particular benefit on the psychic symptoms of GAD.[53,69,70] The size of effect of venlafaxine (mean HAM-A score with venlafaxine minus the mean score with placebo) at 8 weeks in 5 placebo-controlled studies ranged from 1.6 to 4.2 with a mean effect size from pooled data of 2.78 (Figure 5).[71] This represents a marked and clinically meaningful anxiolytic effect in patients with GAD.[68] This effect is associated with some adverse events, including nausea, dizziness, somnolence, and dry mouth, although the incidence of these events declines markedly during long-term therapy.[68] Additional adverse events that may be associated with long-term venlafaxine therapy include sexual dysfunction and the possibility of elevated blood pressure in some patients.[72]

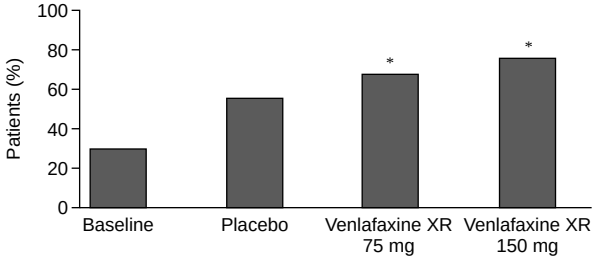
The efficacy of venlafaxine is maintained during long-term treatment. Administration of fixed doses of venlafaxine (37.5–150 mg/day) for 6 months resulted in a dose-dependent, significant reduction in HAM-A total score (mean change = 13.8–16.4 points), compared with placebo (mean reduction = 11 points).[73] This anxiolytic effect has been confirmed where doses of venlafaxine were optimized in a flexible-dose study.[74] Venlafaxine (mean daily dose = 176 mg) produced a reduction in HAM-A total score that was significantly greater than placebo after only 1 week and was sustained for 6 months (Figure 6).[74] Another study showed that after 6 months of drug treatment, 66% of patients receiving venlafaxine were categorized as responders (≥ 50% improvement from HAM-A baseline score), compared with only 39% of those receiving placebo.[70] Furthermore, 43% of patients in the venlafaxine group, compared with only 19% of the placebo group, attained remission from symptoms (HAM-A total score ≤ 7 [Figure 7]).[70] There is also evidence that con-

Figure 7. Proportion of Placebo-Treated and Venlafaxine-Treated Patients That Improved[a]



[a]Based on data from Meoni and Hackett.[70] Response is a ≥ 50% decrease in Hamilton Rating Scale for Anxiety (HAM-A) total score; remission is HAM-A total score ≤ 7.
*p < .001.
†p = .007 venlafaxine vs. placebo (treatment-by-time interaction).

Figure 8. Percentage of Patients With SAS-SR T-Scores ≤ 60[a]



[a]Based on data from Boyer et al.[75] Abbreviations: SAS-SR = Social Adjustment Rating-Self-Report, XR = extended release. A T-score is a standardized measure (derived from a general population) with a mean of 50 and a standard deviation of 10 in all samples. At baseline, only 28% of patients with generalized anxiety disorder reported little or no impairment of social functioning (SAS-SR T-score of ≤ 60). After 6 months of treatment with venlafaxine, there was a significant improvement in social functioning as 66% to 75% of patients were classed with an SAS-SR T-score of ≤ 60, compared with 54% of placebo-treated patients.
*p < .05 vs. placebo.

tinued treatment with venlafaxine is associated with continued benefit, as the majority of patients responding to treatment in the short term will go on to remit, and nonresponders may attain a full response with sustained treatment (Figure 7).[70] In addition to improvement in symptoms of anxiety, administration of venlafaxine has been reported to improve social functioning (Figure 8).[75]

OTHER PHARMACOLOGIC APPROACHES TO THE TREATMENT OF GAD

A limited number of studies have evaluated the efficacy of other agents in the treatment of GAD. These have included partial benzodiazepine receptor agonists, a histamine H_1 receptor antagonist, a sigma receptor antagonist, and newer antidepressants.

Partial benzodiazepine receptor agonists, including abecarnil and suriclone, are speculated to retain the anxiolytic efficacy of benzodiazepines but to be devoid of the potential for causing sedation, interacting with other drugs or alcohol, or inducing dependence. The most extensively studied of these agents, abecarnil, produced a rapid anxiolytic effect within 1 week of commencing treatment, which was significantly greater than that attained by placebo and was associated with a 12- to 13-point decrease in HAM-A total score at 4 weeks.[76–79] However, statistical significance in some of these studies has been difficult to demonstrate due to large and variable placebo effects.[77–79] Two 4-week studies have suggested similar anxiolytic properties of suriclone, although these effects were not clearly significant compared with placebo effects.[26,80] Abecarnil administration was associated with drowsiness, dizziness, fatigue, and difficulties in coordination, but there was no withdrawal syndrome on discontinuation.[76,79] However, these agents have not been tested in longer-term studies, and none are currently available for use in the clinic. Other agents investigated for the treatment of GAD include hydroxyzine, opipramol, and the herbal extract kava-kava.[81] Hydroxyzine is a histamine H_1 receptor antagonist used as a sedative, but which is anxiolytic in patients with GAD.[52,82] However, hydroxyzine has only been studied for a 4-week period, and its use over the chronic course of GAD could be limited by the somnolence induced by agents of this class. Opipramol, an antagonist at sigma receptors, has been shown to be superior to placebo and equally effective as alprazolam in the treatment of GAD.[83] However, this agent also blocks dopamine D_2, serotonin 5-HT_2, and histamine H_1 receptors, and hence the precise mechanism of this anxiolytic action is unclear.

The successful use of venlafaxine and other antidepressants in the treatment of GAD suggests that other antidepressants could be useful for this indication. Trazodone and nefazodone, combined serotonin reuptake inhibitors and 5-HT_2 receptor antagonists, have been evaluated in 2 separate 8-week studies of patients with GAD. Moderate to marked improvement was reported in 69% of trazodone-treated patients, compared with 47% of those receiving placebo, and the anxiolytic effect was comparable with diazepam.[21] However, adverse events related to an anticholinergic effect of this agent were noted throughout the study. In an open study, 80% of patients improved after treatment with nefazodone,[84] and anxiolytic effects of nefazodone have been reported in patients with comorbid anxiety and depression.[85,86] However, no longer-term studies have yet confirmed the potential use of nefazodone or trazodone in the treatment of GAD. Future trends may involve the study of other antidepressants as new tar-

gets become identified. These may include corticotropin-releasing factor antagonists, substance P (neurokinin NK_1) receptor antagonists, and metabotropic glutamate receptor (mGLUr) agonists.[14]

CONCLUSION

A review of the current options available for the treatment of GAD leads to fairly clear recommendations. Psychosocial therapies, particularly cognitive therapy, relaxation therapy, and CBT, are effective alone and may enhance the anxiolytic benefit provided by a pharmacotherapeutic approach. Of the medications available, antidepressants are more effective than benzodiazepines and are devoid of the complicating adverse events. Thus, although benzodiazepines may be useful for short-term management of anxiety, second-generation antidepressants, of which only venlafaxine and paroxetine are indicated for GAD, should be seen as the first-line choice for treatment. There is now recognition that the goal of treatment for anxiety disorders should not simply be a response, but resolution of symptoms and restoration of normal function.

Drug names: alprazolam (Xanax and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), diazepam (Valium and others), hydroxyzine (Atarax and others), lorazepam (Ativan and others), nefazodone (Serzone), paroxetine (Paxil), venlafaxine (Effexor).

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