Overview of Different Pharmacotherapies for Attaining Remission in Generalized Anxiety Disorder

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γ-Aminobutyric acid (GABA), serotonin (5-HT), and norepinephrine (NE) have each been implicated in the putative pathophysiology of anxiety, and patients with generalized anxiety disorder (GAD) demonstrate dysregulation of these neurotransmitters. In addition, neurobiological studies have demonstrated that these neurotransmitter systems are extensively interrelated. As a result, drugs that affect serotonergic systems may also, directly or indirectly, affect other neurotransmitter systems including GABA and NE. In recent years, clinical pharmacology studies have demonstrated that pharmacotherapeutic agents that target more than one neurotransmitter system are more effective than agents that target a single system, presumably due to synergistic mechanisms. Agents that modulate more than one neurochemical have a broader spectrum of action and may facilitate the attainment of remission among patients with moderate to severe GAD, who are likely to have comorbid psychiatric illnesses such as depression. Preclinical and clinical data supporting the role of GABA, 5-HT, and NE in the pathophysiology of GAD are reviewed here. The pharmacotherapeutic agents that modulate these neurotransmitter systems and have been proved efficacious in reducing the symptoms associated with GAD are also summarized.
(J Clin Psychiatry 2001;62[suppl 19]:11–19)

Generalized anxiety disorder (GAD) is characterized by the presence of clinically significant uncontrollable worry or anxiety that persists more days than not for at least 6 months. The constant anxiety about multiple areas of life often manifests with attendant symptoms such as fatigue, restlessness, cognitive difficulties, irritability, muscle tension, and insomnia. A diagnosis of GAD may be excluded if the anxiety does not occur independently of a general medical condition or if it is deemed to be related to physiologic effects of drugs of abuse or toxins.[1] The anxiety and symptomatology of GAD result in significant social impairment and dysfunction, and quality of life is diminished.[2]

GAD typically has a gradual, early- to mid-life onset, with symptoms that wax and wane over the years.[3,4] In addition, individuals with GAD are likely to have comorbid Axis I or Axis II disorders at either initial clinical presentation or later in life.[2–5] Such comorbidity usually exacerbates the impairment associated with GAD.[3,6] Hence, the chronic and debilitating nature of GAD intensifies the need to evaluate the efficacy of treatment options. Numerous pharmacotherapeutic agents have been used in treating GAD. However, these agents may vary in their acute and long-term treatment potential.

THE NEUROCHEMISTRY OF ANXIETY AND GAD

γ-Aminobutyric Acid (GABA)

GABA is ubiquitous in the brain as the predominant inhibitory transmitter that suppresses neuronal activity and regulates the release of other neurotransmitters, especially in the hippocampus, substantia nigra, cerebellum, and striatum. The GABA-A receptor is an integral membrane pentomeric complex containing numerous binding sites that allosterically modulates the chloride channel.[7] Of clinical interest is the benzodiazepine site on the GABA-A receptor complex. When benzodiazepines bind to the GABA-A receptor, they potentiate and prolong the synaptic effects of GABA by increasing the amount of time the chloride channel is effectively open.[8] Benzodiazepines therefore potentiate effects of endogenous GABA and, as a corollary, tend to exert optimal effects in GABA-rich areas of the brain.[7]

Patients with GAD exhibit less benzodiazepine-induced sedation, suggesting an altered sensitivity of central benzodiazepine receptors.[9] Changes in peripheral benzodiazepine receptor binding have been noted in patients with GAD or other forms of anxiety. For example, benzodiazepine receptor binding sites on platelets and lymphocytes are reduced in patients with GAD in comparison to individuals without this disorder.[10–12]

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Presented at the roundtable "Defining Remission in Generalized Anxiety Disorder," which was held June 9, 2000, in Atlanta, Ga., and supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories.
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Long-term treatment with benzodiazepines has been shown to increase peripheral binding sites to normal levels.[10–12] It is unclear if the up-regulation of receptors in response to long-term benzodiazepine treatment has clinical significance or merely reflects benzodiazepine tolerance. Notably, benzodiazepine-induced increases in binding site density occurred only in anxiety patients who had low baseline binding levels and not in healthy controls, implying that the normalization is targeted toward illness-related density reduction and is not merely a pharmacologic phenomenon.[11,12]

Serotonin (5-HT)

Serotonergic neurons are located mainly in dorsal and median raphe nuclei of the brain stem and project throughout the brain, including the hypothalamus, cortex, hippocampus, and amygdala.[13,14] The 5-HT projections to primarily limbic areas have been hypothesized to facilitate conditioned fear and inhibit reactions associated with impending danger, pain, or asphyxia.[15] Neuropharmacologic findings to date support the notion that 5-HT may be a neurobiological substrate in anxiety and depression (see review by Eison[16]). Pharmacologic manipulations of the serotonergic system in animal models indicate that different 5-HT mechanisms (presumably due to 5-HT receptor specificities)[17] are involved in the development of anxiety.[18,19] The 5-HT_{1A} receptor subtype, in particular, has been shown to be instrumental in the genesis of anxious behavior in animal models.[20,21] Experiments using knockout mice have demonstrated concurring behavioral data, providing compelling evidence of the pivotal role of 5-HT receptors in the anxious state.[22–25] The role of 5-HT_{1A} receptors in anxiety has been validated in humans, as evidenced by results from clinical trials of buspirone (a 5-HT_{1A} agonist) in patients with GAD.[26–28]

Antagonism or blockade of 5-HT_2 receptors may also alleviate anxiety and avoidance behaviors observed in animal models of anxiety, particularly through action on 5-HT_2 receptors in the forebrain.[29] However, the utility of serotonergic agents in the treatment of GAD is not well established.[30–32]

Further proof of a serotonergic pathophysiology in GAD arises from findings that lower levels of 5-HT in cerebrospinal fluid[33] and anomalous platelet binding of 5-HT are apparent in patients with GAD as compared with controls.[34] These findings, as well as the accumulating evidence of the efficacy of serotonin reuptake inhibitors in reducing anxiety,[35] suggest that GAD represents a neurochemical imbalance involving 5-HT—a notion consistent with findings from studies involving pharmacologic manipulations in animal models of anxiety.[36]

Although the serotonergic system is considered one of the main neuropathways involved in anxiety, 5-HT also has modulatory effects on the noradrenergic system.[16,37] The interaction between 5-HT and norepinephrine (NE) is reciprocal[16,37] and therefore may play an important role in both the etiology of depressive and anxiety disorders and their treatment. In depression, for example, reduced 5-HT levels may indirectly affect levels of norepinephrine or other neurotransmitters.[37] Moreover, 5-HT has direct effects on 5-HT receptors localized on noradrenergic cells of the locus ceruleus.[16]

Norepinephrine

Noradrenergic projections originating from neurons in the locus ceruleus are widely distributed in the brain, notably in the cortex, hippocampus, amygdala, septum, thalamus, and hypothalamus.[38] NE facilitates the sympathetic response, i.e., physiologic and behavioral adaptations to stress, alarm, and threat. Consequently, noradrenergic dysfunction leads to altered states of fear and arousal.[39] Several lines of evidence suggest that abnormalities in noradrenergic function may underlie pathologic anxiety. Plasma NE levels have been shown to be higher in patients with GAD compared with depressed patients and controls.[40] In the same study, the B_{max} for ^{3}H-yohimbine (an α_2-adrenoceptor antagonist) was found to be lower in patients with GAD, suggesting a decreased number of α_2-adrenoceptors, presumably in response to increases in circulating NE levels.[40] The decreased density of α_2-adrenoceptor binding sites in platelets of patients with GAD concurs with these findings.[41]

In another study, the administration of the α_2-adrenoceptor agonist clonidine resulted in a blunted growth hormone response (compared with controls) that is believed to be a consequence of α_2-adrenoceptor hyposensitivity in GAD.[42] Also consistent with this hypothesis is the finding that yohimbine, an α_2-adrenoceptor antagonist, attenuates the 3-methoxy-4-hydroxyphenylglycol (MHPG, a noradrenergic metabolite) response among patients with GAD.[43] It is unclear, however, if the physiologic abnormalities associated with α_2-adrenergic receptor function are due to receptor hyposensitivity or a reduction in the density of α_2-adrenergic receptor binding sites.

OTHER ETIOLOGIC VARIABLES IN GAD: IMPLICATIONS FOR TREATMENT

Although several neurochemical and neuroendocrine systems appear to be involved in regulating anxiety, other factors such as genetics or psychosocial and environmental milieu may contribute to the etiology of GAD.[2,44] Early childhood stressors or traumas, for example, are predisposing factors for the development of GAD.[2]

Limbic regions of the brain, especially the amygdala, have been associated with the modulation of autonomic and central hyperarousal and responses to psychosocial stressors that are pronounced in anxiety disorders.[39,44–46] Because of the dynamic interactions among various neuroregulators (especially involving the monoaminergic

system), the treatment of GAD does not merely "correct" a single neurotransmitter dysfunction. Rather, pharmacotherapeutic interventions, in particular, initiate a cascade of biochemical processes that typically leads toward a more balanced neurochemical state. Hence, the efficacy of pharmacotherapeutic agents for the treatment of GAD (e.g., antidepressants) may involve adaptive neurochemical changes at the synaptic level.[16]

It is noteworthy that previous studies evaluating the rate of remission in patients with GAD within a 5-year period have indicated low remission rates despite treatment.[47,48] The pharmacotherapeutic agents used in these studies, however, did not include newer generation agents.[47] Data from recent long-term studies of patients with GAD using the dual-action serotonin-norepinephrine reuptake inhibitor venlafaxine extended release (XR) have been more encouraging, showing higher rates of remission[49,50] and less discontinuation due to lack of efficacy[51] (see article by Sheehan[52] in this supplement).

PHARMACOTHERAPEUTIC APPROACHES TO GAD

Benzodiazepines

The effectiveness of benzodiazepines in symptom reduction in GAD is well documented.[53–56] As anxiolytics, benzodiazepines potentiate the inhibitory effects of GABA[7] through their action on the GABA-A receptor. GABA decreases the firing rate of neurons in the locus ceruleus, thereby minimizing the excessive noradrenergic activity observed in anxiety.[37] GABA also modulates the release and turnover rates of monoamines in limbic and brain stem regions, which are involved in fear, stress, and anxiety.[7] Thus, by enhancing the inhibitory effects of GABA, benzodiazepines indirectly regulate the monoaminergic neurotransmitter systems in a manner that elicits anxiolytic effects.[7]

The half-lives of benzodiazepines range between 1 hour and 120 hours.[4,8] The differences in this pharmacokinetic property of benzodiazepines have important ramifications relating to symptoms associated with treatment discontinuation, although the various benzodiazepines appear to have similar efficacy in the treatment of GAD.[4] Some benzodiazepines, such as diazepam and chlordiazepoxide, which are slowly metabolized and have multiple active metabolites, are associated with fewer intradose symptom breakthroughs, have less adverse consequences of missing a dose, and have the capacity for a more rapid tapering schedule. Clonazepam, a newer generation high-potency benzodiazepine, is preferred by many clinicians because of the pharmacologic advantages associated with its longer half-life. In contrast, oxazepam and lorazepam are more rapidly metabolized and have no active metabolites. These agents are beneficial for certain patients who only need brief, intermittent anxiolysis and for "slow metabolizers," such as the elderly and patients with liver disease.

Although the half-life of benzodiazepines does not seem to influence anxiolytic efficacy, this pharmacokinetic property influences the intensity, duration, and severity of withdrawal symptoms and therefore should be a treatment consideration.[4] Moreover, the lipid solubility of a particular benzodiazepine agent should be assessed before use, because high lipid solubility (e.g., with diazepam) hastens the onset of drug effects.[8]

Adverse effects of benzodiazepines include sedation and psychomotor impairment. However, tolerance to these adverse effects usually develops, often without affecting the degree of anxiolysis. Moreover, discontinuation syndrome is associated with benzodiazepine treatment withdrawal.[4] Common symptoms of benzodiazepine withdrawal include restlessness, anxiety, agitation, irritability, unsteadiness, muscle tension, depression, photophobia, auditory hypersensitivity, tremor, and increased pulse.[4] Of greater concern is the fact that approximately 63% to 81% of patients with GAD have been shown to relapse within weeks or months of benzodiazepine discontinuation.[8] To avoid the onset of adverse effects, discontinuation should be done by gradually tapering the dose of benzodiazepine.[57]

While the efficacy of benzodiazepines in reducing the symptoms of GAD has been frequently documented, it is noteworthy that benzodiazepines tend to relieve somatic[58] and autonomic symptoms more effectively than psychic symptoms of anxiety.[59,60] In further defining GAD as a distinct psychiatric disorder, the DSM-IV emphasizes that worry, apprehension, and other psychic symptoms are hallmark symptoms of GAD. Thus, earlier studies examining the efficacy of benzodiazepines in patients who were included in the studies based on diagnostic criteria predating the DSM-IV may have misleading conclusions regarding treatment efficacy.[59] This concern is supported by findings in some studies that less than half of GAD patients showed a marked improvement with benzodiazepine treatment,[4,8] although these findings may have been related to confounding factors such as the presence of comorbid psychiatric disorders (e.g., depression). Because benzodiazepines do not prevent depression from emerging and may even exacerbate or precipitate depression,[8,61] the usefulness of monotherapeutic benzodiazepine treatment for most patients with GAD is limited, especially since epidemiologic studies have shown that GAD is typically comorbid with other psychiatric illnesses, notably major depression.[62–64] Specific symptoms and comorbid disorders of individual patients with GAD should be evaluated before prescribing benzodiazepines, and augmentation treatment for the depressive component of the illness may be considered.

The recurrence of anxiety symptoms occurs significantly more often with benzodiazepines in comparison to nonbenzodiazepine anxiolytics.[4] Moreover, tolerance,

discontinuation syndromes, and physical dependence discourage the long-term use of benzodiazepines as monotherapy for GAD.[65] However, because of their rapid onset of action and efficacy in somatic and autonomic symptoms, benzodiazepines may be especially useful in GAD when conspicuous adrenergic symptoms or other acute components of anxiety, such as panic attacks, are present,[66] or as an adjunctive therapy.

5-HT_{1A} Agonists: Buspirone

After benzodiazepines, buspirone (an azapirone) was the first pharmacotherapeutic agent to gain U.S. Food and Drug Administration (FDA) approval for GAD. The anxiolytic effect of buspirone is attributed to the net attenuation of 5-HT activity.[16] Buspirone is primarily an agonist at presynaptic 5-HT_{1A} receptors and a partial agonist at postsynaptic 5-HT_{1A} receptors in several brain regions known to be involved in stress, fear, and anxiety, such as the raphe nucleus, cortex, amygdala, and hippocampus[67]; it also acts on 5-HT_2 receptors.[16,67,68] Additionally, buspirone is a dopamine agonist, possessing a weak affinity for both dopamine D_2 and D_3 receptor subtypes.[67]

Buspirone is typically administered in a dosage range of 20 to 60 mg/day.[69] It has been shown to be effective and safe in the treatment of GAD, maintaining efficacy over the course of months.[3,59] However, there is a 3- to 4-week lag time before anxiolytic efficacy is achieved. Thus, although buspirone is considered to be as effective as benzodiazepines, it takes several weeks before equal efficacy is apparent.[67] This slow onset of anxiolytic action may be problematic in some patients because of the inherently acute nature of anxiety.

Unlike benzodiazepines, buspirone is more effective for the psychic symptoms of GAD, such as apprehension and worry, as well as depressive symptoms, although it is not especially effective for somatic or autonomic symptoms of anxiety.[3,59] Nevertheless, because buspirone acts as a partial agonist, the specific action of buspirone is dependent on the perisynaptic neurochemical milieu within the brain.[16] Buspirone may be especially useful in elderly patients who are more sensitive to benzodiazepine use. In addition, it may be useful and effective in combination with benzodiazepines, resulting in a synergistic effect that is greater than the effect of either drug treatment alone.[70]

Unlike benzodiazepines, buspirone does not induce sedation, psychomotor or cognitive impairment, or physical dependence or tolerance, and it does not interact with alcohol.[3,4,68,69] Side effects associated with buspirone include dizziness, headaches, and nausea, which are generally considered to be mild.[68]

Buspirone is not as effective in other anxiety disorders besides GAD,[37,71,72] i.e., buspirone has not been clearly shown to be effective in panic disorder and social phobia when compared with reference standards. [6,71] It is useful as an adjunctive agent with other psychotropic medications.[71,73] The dichotomous effect of buspirone in GAD and panic disorder supports the distinctiveness of these disorders, suggesting differences in the neuropathophysiology of each,[68] despite the fact that GAD is frequently comorbid with other disorders, including panic. The slow onset of action of buspirone,[74] the apparent lack of a dose-response relationship,[75] and the accumulating data regarding its lackluster anxiolytic potency have diminished the initial excitement toward this agent.[69]

Monoamine Oxidase Inhibitor (MAOI) Antidepressants

MAOIs act by inhibiting the breakdown of monoamines, thereby altering the amount of available neurotransmitter. MAOIs have been proved effective in depression and especially in "atypical depression," which is often accompanied by anxious features such as panic.[37] MAOIs are especially effective in social phobia (both discrete and generalized) but may have a more limited utility in patients with posttraumatic stress disorder (PTSD).[61] Of the anxiety disorders, MAOIs also have notable efficacy in panic disorder, since they effectively block the autonomic aspects of panic.[76] Clinically, MAOIs are as effective as tricyclic antidepressants (TCAs) in the treatment of panic and may be especially useful if panic is comorbid with major depression.[61] It is not clear what role MAOIs might have in treating GAD; however, caution should be exercised if administering agents that could induce behavioral excitation[76] to an individual with GAD. In addition, the drug and food interaction potential in combination with the serious side effect profile of MAOIs renders them less clinically desirable than other possible treatment options.[37,61]

Tricyclic Antidepressants

TCAs modulate the reuptake of 5-HT and/or NE, having varying selectivity for these neurotransmitters. TCAs are effective in the treatment of depression, and some exhibit anxiolytic activity. Imipramine in particular has been used as a standard treatment for panic disorder prior to the introduction of newer antidepressant/anxiolytic agents,[61] while clomipramine has proved efficacious in the treatment of obsessive-compulsive disorder (OCD).[61] However, placebo-controlled studies evaluating the efficacy of TCAs in the treatment of GAD are limited, especially with regard to their ability to facilitate the achievement of remission.

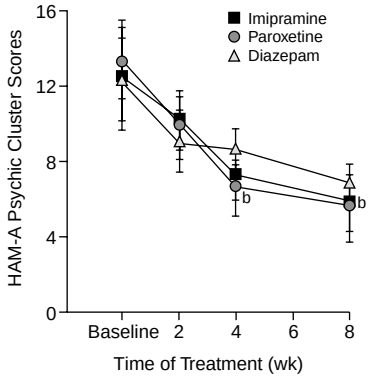
In a placebo-controlled trial designed to examine TCA efficacy in GAD, imipramine was compared with trazodone and diazepam.[77] Diazepam exhibited an onset of action within the first 2 weeks of the study.[77] Trazodone and imipramine were not noticeably effective until after the third week of treatment, but from that point forward, they both were as effective as diazepam.[77] Imipramine appeared more efficacious as an anxiolytic than trazodone.[77]

Diazepam was especially effective in alleviating somatic symptoms, whereas imipramine was more effective in alleviating psychic symptoms. With continued treatment, however, imipramine was also effective for somatic symptoms.[60,77] A study comparing alprazolam with imipramine reported similar trends relating to the time course of symptom improvement and specificity of somatic versus psychic symptoms.[78]

A recent placebo-controlled study of patients with GAD compared the efficacy of alprazolam and opipramol (a strong but nonselective tricyclic, Σ site ligand used widely in Germany).[79] In showing that opipramol was as efficacious as alprazolam, these findings concur with the previously described study that TCAs are efficacious in the treatment of GAD.

Adverse effects associated with TCAs include dry mouth, constipation, orthostatic hypotension, dizziness, somnolence, and weight gain.[4,61] TCA toxicity and potential overdose lethality observed in patients with severe depression are also concerns in treating patients with anxiety disorders.

Figure 1. Hamilton Rating Scale for Anxiety (HAM-A) Psychic Cluster Scores at Baseline and After 2, 4, 6, and 8 Weeks of Treatment With Imipramine, Paroxetine, or 2'-Chlordesmethyldiazepam[a]



[a]Reprinted, with permission, from Rocca et al.[90]
[b]Significant ($p < .05$) between-group differences as assessed by pairwise comparison.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The advantages of SSRIs in treating anxiety are not as well documented as their clinical utility in treating depression. Most of the evidence supporting the usefulness of SSRIs in anxiety disorders comes from studies of patients with panic disorder[80–82] and OCD.[83–84] There are also a few studies demonstrating that SSRIs are useful for PTSD[85–87] and social anxiety disorder.[88,89] There is evolving evidence that at least the SSRI paroxetine is effective in GAD.[90,91]

Rocca and colleagues,[90] using DSM-IV criteria for GAD, compared efficacy of diazepam (a benzodiazepine), imipramine (a TCA), and paroxetine (an SSRI) over an 8-week treatment period. All 3 treatments reduced symptoms of GAD within the first 2 weeks of treatment, with diazepam showing greater results than the other drugs during the first 2-week period.[90] However, imipramine and paroxetine demonstrated significantly better efficacy than diazepam by the fourth week of treatment, particularly in psychic symptoms of anxiety (Figure 1).[90] In a placebo-controlled study, Bellew and colleagues[91] reported that both 20 and 40 mg/day of paroxetine were effective in treating GAD over an 8-week trial. However, paroxetine did not differentiate from placebo until 4 weeks of treatment.[91] A dose-response effect of paroxetine was not apparent using the Hamilton Rating Scale for Anxiety.[91] The utility of paroxetine in long-term maintenance therapy and its potential to achieve and maintain remission in GAD are under study and appear promising.

Overall, SSRIs are safer and more tolerable than TCAs. However, they may cause gastrointestinal distress and sleep disturbances; also, sexual side effects are relatively common.[61]

Nefazodone

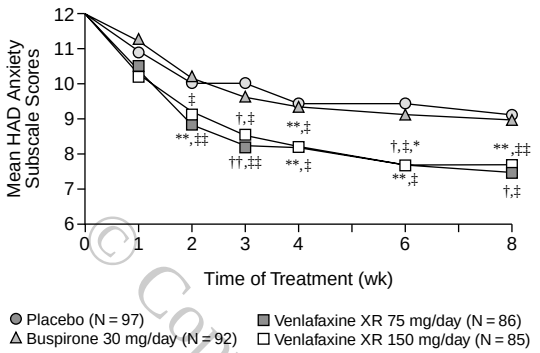
Nefazodone is a newer antidepressant with anxiolytic potential. It acts by blocking the 5-HT_{2A} receptor, antagonizing the 5-HT_{2C} receptor, inhibiting reuptake of 5-HT (at higher doses), and to some extent serving as an adrenergic antagonist.[59,92] In a small, open-label 8-week trial of nefazodone in patients with GAD, 80% reported their symptoms as being at least "much improved."[92] Common side effects of nefazodone included fatigue, drowsiness, headache, and insomnia.[92] Overall, nefazodone was effective and well tolerated.[92] The recommended dosage of ~375 mg/day for treating GAD is similar to effective nefazodone doses used for treating depression.[92] Although nefazodone has been proved effective as an antidepressant, its potential for the attainment and maintenance of remission in the long-term treatment of GAD needs further investigation.

Venlafaxine XR

Venlafaxine XR is a dual 5-HT and NE reuptake inhibitor.[93] It has a unique nontricyclic structure and has little interaction with other neurotransmitter receptors.[94] In addition to its efficacy as an antidepressant, evidence is accumulating that venlafaxine XR is efficacious in the treatment of GAD[50,95,96] (also see reviews by Kelsey[97] and Hackett[98]). In fact, venlafaxine XR is the first antidepressant that is indicated for both depression and GAD. Dosing of venlafaxine XR for treating GAD is similar to its dosing as an antidepressant, with an effective range between 75 and 225 mg/day.[69]

A study by Davidson and colleagues[95] compared the efficacy of 2 agents approved for GAD, venlafaxine XR and buspirone. Based on the Hospital Anxiety and Depression

Figure 2. Mean Hospital Anxiety and Depression (HAD) Anxiety Subscale Scores During 8 Weeks of Treatment With Placebo, Buspirone, or Venlafaxine Extended Release (XR)[a]



[a]Reprinted, with permission, from Davidson et al.[95]
*150-mg/day group.
**p < .05 vs. placebo.
†p ≤ .005 vs. placebo. ††p < .001 vs. placebo.
‡p ≤ .05 vs. buspirone. ‡‡p ≤ .01 vs. buspirone.

anxiety subscale, venlafaxine XR demonstrated significantly greater efficacy over buspirone in patients with GAD but without comorbid depression (Figure 2).[95] In another study comparing the efficacy of venlafaxine XR and fluoxetine in patients with depression and comorbid GAD, venlafaxine XR showed a greater magnitude of effect in both depression and anxiety.[99] This suggests that dual-mechanism agents (i.e., acting on both 5-HT and NE systems) are clinically advantageous in treating a population with comorbid depression and GAD.[99] Consistent with these findings, a pharmacoeconomic study showed that among depressed patients, those receiving venlafaxine had significantly lower rates of concomitant use of anxiolytic medications compared with patients receiving other agents such as TCAs or SSRIs.[100]

Previous long-term studies of GAD[101] have been inconclusive primarily because subjects were evaluated and diagnosed according to the "old" criteria (i.e., DSM-III), which categorized the symptoms of GAD as "residual."[101] The long-term studies using venlafaxine XR are the first placebo-controlled attempts at evaluating the pharmacotherapeutic efficacy of venlafaxine over an extended period using the DSM-IV criteria for GAD. Venlafaxine XR has been shown to facilitate remission in patients with GAD (see article by Sheehan[52] in this supplement). The studies that have evaluated remission in patients with GAD following venlafaxine XR treatment used 70% symptom improvement from baseline as their criterion for efficacy, a requirement that is more stringent than the standard response measure of 50% improvement over baseline. In addition, recent studies have provided evidence that venlafaxine XR, with an anxiolytic effect apparent within 1 week of treatment, is useful for long-term maintenance therapy in GAD.[50] Thus, the onset of action of venlafaxine XR occurs sooner than the typical 4-week time frame reported for other antidepressants and anxiolytics used to treat GAD.

The lack of interaction of venlafaxine XR with cholinergic, histaminergic, and α_1-adrenergic receptors[102] limits side effects and increases tolerability. Nausea and somnolence are the common side effects associated with venlafaxine treatment. These are considered mild and tend to dissipate over the first few weeks of treatment. In support of its tolerability, venlafaxine XR was shown to have a lower discontinuation rate than the SSRIs and nefazodone.[103] Hence, the early onset of action, long-term efficacy (i.e., facilitating remission), and safety and tolerability profile of venlafaxine XR are compelling reasons for its use as first-line therapy in patients with GAD.

CONCLUSION

Current anxiolytic pharmacotherapeutic options include varying mechanisms of action and illustrate the dynamic state of central neuroregulatory systems, particularly involving GABAergic, serotonergic, and noradrenergic neurotransmission. Monoaminergic transmitter systems are also implicated in depressive states, suggesting that depression and anxiety are spectral components of a broad neuropathologic state.

The pharmacotherapy of GAD is not as well established as that for depression and other anxiety states such as panic disorder and OCD. This may be partly due to the fact that, until about 2 decades ago, GAD was considered a prodrome of depression, not surprising given the high rate of comorbid depression that is typically preceded by GAD. Many traditional antidepressants (e.g., TCAs and MAOIs) and later generation antidepressants (e.g., nefazodone, paroxetine [an SSRI]) have demonstrated efficacy in the treatment of GAD, although data on the long-term utility of these agents are lacking. Nonetheless, the better tolerability of the SSRIs relative to traditional agents has led to an increase in their use in GAD. It is noteworthy, however, that TCAs and venlafaxine XR also have been shown to be efficacious in the treatment of severe depression cases, which have a high likelihood of comorbidity with anxiety disorders such as GAD. Pharmacologically, TCAs and venlafaxine XR have dual mechanisms of action involving both 5-HT and NE systems. However, the tolerability and safety of venlafaxine XR are superior to that of TCAs; venlafaxine XR has also been shown to have an earlier onset of action than TCAs. In light of mounting data supporting the superiority of dual-mechanism agents in treating depression and anxiety,[104,105] an antidepressant such as venlafaxine XR, which acts on both 5-HT and NE systems and has been shown to have an early onset of action, long-term efficacy, and favorable safety/tolerability profile, should be a first-line therapeutic choice.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), chlordiazepoxide (Librium and others), clomipramine (Anafranil and

others), clonazepam (Klonopin and others), clonidine (Catapres and others), fluoxetine (Prozac), diazepam (Valium and others), lorazepam (Ativan and others), nefazodone (Serzone), oxazepam (Serax and others), paroxetine (Paxil), venlafaxine (Effexor), yohimbine (Yocon and others).

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