Qualitative Review of SNRIs in Anxiety

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Anxiety disorders pose a problem for a significant number of individuals, with a 1-year prevalence rate estimated at 13.1% to 17.1%. Many pharmacologic agents have been used to treat anxiety disorders, and among those in current use are newer benzodiazepines (alprazolam), azapirones (buspirone), selective serotonin reuptake inhibitors (paroxetine and sertraline), and venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI). The likely role of abnormal serotonergic neurotransmission in anxiety is widely supported, while the role of norepinephrine is less clear. Still, many lines of evidence support the hypothesis that a perturbation in norepinephrine neurotransmission contributes to the symptoms of anxiety. Therefore, it is conceivable that modulation of both serotonin and norepinephrine systems by dual-reuptake inhibitors may be an advantage in the treatment of anxiety disorders. Given this, the current review examines evidence on the possible role of venlafaxine in the treatment of anxiety disorders. From this review it is clear that venlafaxine is as efficacious as selective serotonin reuptake inhibitors in treating anxiety, with comparable tolerability. Future research will be valuable in determining if antidepressants that combine pharmacologic actions on serotonergic and noradrenergic systems have advantages over more selective agents in treating anxiety disorders.

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Anxiety disorders, including generalized anxiety disorder (GAD), social anxiety disorder, panic disorder, posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD), affect approximately 19 million Americans between 18 and 54 years of age.[1] The 1-year prevalence rate for all anxiety disorders is estimated at 13.1%[1] to 17.1%.[2] The most common anxiety disorder is social anxiety disorder, followed in decreasing order of prevalence by simple phobias, GAD, panic disorder, OCD, and PTSD.[2] According to the U.S. National Institute of Mental Health (NIMH), based on information derived from the 1998 U.S. Census, social anxiety disorder affects 5.3 million Americans, PTSD affects 5.2 million, and GAD affects 4 million, while OCD affects 3.3 million, and panic disorder affects 2.4 million Americans.[1]

Many pharmacologic treatments have been used to treat anxiety disorders, including benzodiazepines, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and newer single-acting and dual-acting antidepressants. The benzodiazepine diazepam has been shown to be effective, with a rapid onset of action, but is considered a less favorable option for long-term treatment due to the potential for withdrawal, physical dependence, memory disturbances, sleepiness, and lethargy.[3–6] TCAs, such as imipramine, and MAOIs are effective anxiolytics, but their untoward side effects and safety concerns render them less desirable to patients.[3–5,7] Although newer benzodiazepines (alprazolam) and azapirones (buspirone) remain in use for the treatment of anxiety, antidepressants including selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine and sertraline), and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have largely replaced other anxiolytic agents as first-line treatment for anxiety disorders due to the better safety and side effect profile.[6]

Substantial evidence demonstrates that major depressive disorder (MDD) is associated with dysregulation of both serotonin and norepinephrine neurotransmission, and clinical observations demonstrate a significant degree of overlap in symptoms associated with MDD and anxiety disorders (Figure 1). Although the precise mechanisms underlying the pathogenesis of anxiety remain unclear, evidence supports decreased serotonergic function in depression and anxiety.[8] This includes evidence from studies of anxiety disorder patients that have shown reduced levels of serotonin in the cerebrospinal fluid.[9] Additionally, there have been reports of reduced serotonin transporter binding in patients with GAD.[10] Further, dysregulation of serotonergic neurotransmission is believed to play a role in the manifestation of symptoms of anxiety.[8] Consistent with these notions, antidepressants that

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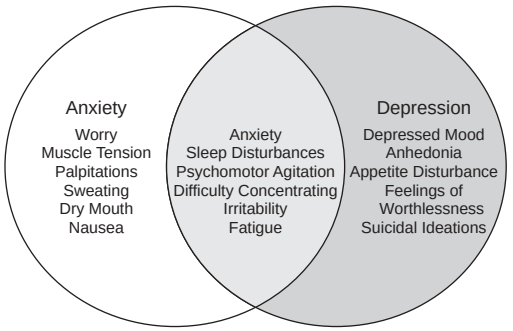
Figure 1. Overlapping Symptoms of Depression and Generalized Anxiety Disorder[a]



[a]Based on Nutt.[86]

enhance serotonergic neurotransmission, such as the SSRIs, have been found to be effective in treating some anxiety disorders.[6,8,11,12]

The role of norepinephrine in anxiety is less clear, but many lines of evidence support the hypothesis that norepinephrine neurotransmission is involved in anxiety.[8] Norepinephrine has been shown to modulate activity in regions of the brain that are involved in anxiety, such as the amygdala.[13–16] In addition, increases in 3-methoxy-4-hydrophenylglycol (MHPG; a metabolite of norepinephrine)[17] and hypersecretion of norepinephrine in plasma and CSF[17–19] have been associated with anxiety states. Clinical evidence, including findings from studies that have evaluated the anxiolytic efficacy of agents that modulate noradrenergic neurotransmission, is consistent with norepinephrine involvement in anxiety disorders.[4]

DUAL-ACTING AGENTS IN THE TREATMENT OF ANXIETY

Review of Clinical Data

Since there is some neurobiological evidence supporting the involvement of both serotonin and norepinephrine in the pathogenesis and treatment of anxiety disorders, it is conceivable that antidepressants that modulate the activity of both neurotransmitters may be associated with therapeutic advantages over more selective agents. The major aim of the current review is to examine the results from all randomized, controlled trials (RCTs) in which antidepressants with noradrenergic activity, including the SNRIs venlafaxine and duloxetine, the norepinephrine reuptake inhibitor (NRI) reboxetine, and the TCA desipramine, have been examined in the treatment of anxiety disorders. Milnacipran, another SNRI, has not been evaluated in RCTs in the treatment of anxiety. To date, the majority of these RCTs have evaluated venlafaxine, which has been studied in the treatment of GAD,[20–25] comorbid GAD and MDD,[26–29] social anxiety disorder,[30–33] panic disorder,[34,35] PTSD,[36] and OCD.[37] Data are also available from a small placebo-controlled trial of reboxetine in treating panic disorder[38] and a pooled analysis of the efficacy of duloxetine in treating anxiety symptoms as secondary outcome measures in clinical trials of MDD.[39] Reboxetine has also been evaluated in open-label studies for the treatment of panic disorder and social anxiety disorder.[40,41] Several small studies are available that have assessed the efficacy of desipramine against placebo and active comparators in patients with depression and anxiety in a variety of settings.[42–47]

Clinical Efficacy in Individual Disorders

Generalized anxiety disorder. Three short-term (8-week) placebo-controlled RCTs, including 2 studies with active comparators, have evaluated the efficacy of venlafaxine extended release (ER) in the treatment of GAD (Table 1).[22,24,25] In one of the active comparator studies,[25] patients were given placebo (N = 97) or treated with venlafaxine ER 75 mg/day (N = 185), venlafaxine ER 150 mg/day (N = 169), or diazepam 15 mg/day (N = 89). A substantial placebo response led to a lack of significant between-group differences on any primary outcome measure and made it difficult to determine whether there was a difference either venlafaxine ER or diazepam had on efficacy in this study population.[25] Because a high degree of placebo response is not unexpected in this type of clinical trial,[48,49] preplanned secondary analyses were included to evaluate data from the study centers that had significant improvements of diazepam over placebo. The results of these analyses indicated that both diazepam- and venlafaxine ER–treated patients had significantly better responses than placebo-treated patients on all primary outcome measures.[25] In the other short-term active comparator study, administration of venlafaxine ER 75 mg/day (N = 64) or 150 mg/day (N = 55) for 8 weeks resulted in a reduction in the mean Hamilton Rating Scale for Anxiety (HAM-A) total score that was significantly greater than the reductions associated with buspirone (30 mg, N = 69) or placebo (N = 68).[24] Taken together, these studies suggest that venlafaxine ER is efficacious in short-term treatment of GAD.

Long-term studies examined whether the clinical efficacy of venlafaxine in treating GAD is maintained for 6 months or longer (Table 1).[21,23] In one study, treatment with venlafaxine ER at fixed doses of 37.5 mg/day (N = 140), 75 mg/day (N = 134), or 150 mg/day (N = 137) for 6 months was compared with placebo (N = 130).[21] The results showed a dose-dependent, significant reduction in HAM-A total scores, compared with placebo. In another 6-month study, patients were given placebo (N = 127) or flexible doses of venlafaxine ER from 75 to 225 mg/day (N = 124).[23] This study confirmed the anxiolytic effects of venlafaxine ER (mean daily dose = 176 mg), with a significantly greater reduction in HAM-A total scores in venlafaxine-treated patients compared with the placebo

Table 1. Randomized, Double-Blind, Placebo-Controlled Studies of Venlafaxine Treatment of Generalized Anxiety Disorder

Study	Duration	Treatment Group, Daily Dose, (N)	Primary Outcome Measure(s)	Results at Endpoint
Rickels et al, 2000[22]	8 wk	Venlafaxine ER 75 mg (N = 86) Venlafaxine ER 150 mg (N = 81) Venlafaxine ER 225 mg (N = 86) Placebo (N = 96)	HAM-A total score HAM-A psychic anxiety CGI-S CGI-I	Venlafaxine ER 75 mg: No statistically significant differences vs placebo Venlafaxine ER 150 mg: Significantly greater improvement vs placebo on 1 measure (HAM-A psychic anxiety) Venlafaxine ER 225 mg: Significantly greater improvement vs placebo on all 4 measures
Hackett et al, 2003[25]	8 wk	Venlafaxine ER 75 mg (N = 185) Venlafaxine ER 150 mg (N = 169) Diazepam 15 mg (N = 89) Placebo (N = 97)	HAM-A total score HAM-A psychic anxiety HAD anxiety subscale CGI-I	Venlafaxine ER 75 mg, venlafaxine ER 150 mg, diazepam: Greater, but not statistically significant, improvement vs placebo on all measures (Significant differences favoring venlafaxine ER [both doses] vs placebo on all primary measures in secondary analysis of selected study centers)
Davidson et al, 1999[24]	8 wk	Venlafaxine ER 75 mg (N = 64) Venlafaxine ER 150 mg (N = 55) Buspirone 30 mg (N = 69) Placebo (N = 68)	HAM-A total score HAM-A psychic anxiety CGI-S CGI-I	Venlafaxine ER 75 mg: Significantly greater improvement vs placebo on 3 of 4 measures (all but HAM-A total score); significantly greater improvement vs buspirone on 1 measure (CGI-S) Venlafaxine ER 150 mg: Significantly greater improvement vs placebo on 2 of 4 measures (HAM-A psychic anxiety and CGI-I) Buspirone: No statistically significant differences vs placebo
Allgulander et al, 2001[21]	6 mo	Venlafaxine ER 37.5 mg (N = 140) Venlafaxine ER 75 mg (N = 134) Venlafaxine ER 150 mg (N = 137) Placebo (N = 130)	HAM-A total score HAM-A psychic anxiety HAD anxiety subscale CGI-I	Venlafaxine ER 37.5 mg: Significantly greater improvement vs placebo on 3 of 4 measures (all but CGI-I) Venlafaxine ER 75 mg and venlafaxine ER 150 mg: Significantly greater improvement vs placebo on all measures
Gelenberg et al, 2000[23]	6 mo	Venlafaxine ER 75–225 mg (N = 124) Placebo (N=127)	HAM-A total score HAM-A psychic anxiety HAD anxiety subscale CGI-I	Venlafaxine ER: Significantly greater improvement vs placebo on all measures

Abbreviations: CGI-I = Clinical Global Impressions-Improvement, CGI-S = Clinical Global Impressions-Severity of Illness, ER = extended release, HAD = Hospital Anxiety and Depression Rating Scale, HAM-A = Hamilton Rating Scale for Anxiety.

group. This difference was significant beginning after the first week and continued through 28 weeks.

Evidence of a dose-response effect with venlafaxine ER in treating GAD has been inconsistent. Two studies did not show clear evidence of a dose-response relationship using doses of 75 mg/day and 150 mg/day.[24,25] Other studies with 3 doses[21,22] suggest that there is a dose-response effect with venlafaxine in treating the symptoms of GAD. One showed a trend toward greater efficacy with doses progressing from 37.5 mg/day to 75 mg/day, and up to 150 mg/day[21]; the other found a significant trend toward greater efficacy with increasing doses on 4 main efficacy variables.[22] Taken together, these data suggest that a dose of venlafaxine ER of 150 mg may be optimal.

Social anxiety disorder. A variety of drug and non-drug therapies have been studied for treatment of social anxiety disorder, with SSRIs and cognitive-behavioral therapy among the most commonly used.[50,51] Overall, SSRIs produce a therapeutic response in 50% to 60% of patients,[52] with fewer patients achieving remission (one suggested definition of remission is a Liebowitz Social Anxiety Scale [LSAS] score of 30 or less).[53] Cognitive-behavioral group therapy has similar outcome rates.[54] Evidence also suggests that dual-acting SNRIs may be equally effective as SSRIs in treating social anxiety disorder.

Open-label studies suggested a possible clinical benefit with venlafaxine.[55,56] Two double-blind placebo-controlled RCTs[33,57] have examined the efficacy of venlafaxine ER in the short-term (12 weeks) treatment of social anxiety disorder. Findings were similar for both studies: treatment with flexible-dose venlafaxine ER (75–225 mg/day) was significantly more efficacious than placebo in alleviating the symptoms of social anxiety disorder, as measured by LSAS total scores, Social Phobia Inventory (SPIN) scores, Clinical Global Impressions-Severity of Illness (CGI-S) scores, and response based on CGI-Improvement (CGI-I) score of 1 or 2.[33,57] In addition, 2 short-term RCTs have been conducted to compare venlafaxine ER, paroxetine, and placebo head-to-head in patients with social anxiety disorder (Table 2).[30,32] In both studies, patients were treated with venlafaxine ER (75–225 mg/day), paroxetine (20–50 mg/day), or placebo for 12 weeks. Venlafaxine ER and

Table 2. Randomized, Double-Blind, Placebo-Controlled Studies of Venlafaxine Treatment of Social Anxiety Disorder

Study	Duration	Treatment Group, Daily Dose, (N)	Primary Outcome Measure	Results at Endpoint
Allgulander et al, 2004[30]	12 wk	Venlafaxine ER 75–225 mg (N = 122) Paroxetine 20–50 mg (N = 122) Placebo (N = 119)	LSAS total score	Venlafaxine ER, paroxetine: Significantly greater improvement vs placebo (both $p \leq .001$) No significant differences between treatment groups on primary or secondary efficacy variables
Liebowitz et al, 2004[32]	12 wk	Venlafaxine ER 75–225 mg (N = 103) Paroxetine 20–50 mg (N = 102) Placebo (N = 113)	LSAS total score	Venlafaxine ER, paroxetine: Significantly greater improvement vs placebo (both $p \leq .001$) No significant differences between active treatment groups on primary efficacy variables (significant difference in favor of venlafaxine ER over paroxetine on 1 secondary variable, Social Phobia Inventory, at weeks 1 and 2; $p < .05$)
Rickels et al, 2004[33]	12 wk	Venlafaxine ER 75–225 mg (N = 126) Placebo (N = 135)	LSAS total score	Venlafaxine ER: Significantly greater improvement vs placebo ($p < .01$)
Stein et al, 2004[31]	28 wk	Venlafaxine ER 75 mg (N = 131) Venlafaxine ER 150–225 mg (N = 130) Placebo (N = 134)	LSAS total score	Venlafaxine ER 75 mg, venlafaxine ER 150–225 mg, venlafaxine ER groups combined: Significantly greater improvement vs placebo (all $p < .001$)
Liebowitz and Mangano, 2002[57]	12 wk	Venlafaxine ER 75–225 mg (N = 133) Placebo (N = 138)	LSAS total score	Venlafaxine ER: Significantly greater improvement vs placebo ($p < .001$)

Abbreviations: ER = extended release, LSAS = Liebowitz Social Anxiety Scale.

paroxetine treatment resulted in significantly greater improvement than placebo in LSAS total scores, SPIN scores, CGI-S scores, and response rates (based on CGI-I score of 1 or 2). Significant differences between venlafaxine ER and paroxetine treatment were observed in 1 study,[30] in which there was significantly greater improvement in SPIN scores with venlafaxine ER compared with paroxetine at weeks 1 and 2 (Table 2).[32]

The efficacy of venlafaxine ER in treating patients with social anxiety disorder has also been examined in a 28-week long-term RCT (Table 2).[31] In this large-scale study, 2 venlafaxine ER dose regimens were used, with 75 mg/day as a fixed dose (N = 131) and a flexible dose range from 150–225 mg/day (N = 130), which were both compared with placebo (N = 134). Improvements in the primary outcome measure, LSAS total score, were significantly better in both venlafaxine ER treatment arms compared with placebo. The response rate was 58% for the venlafaxine ER groups and was significantly greater than the response rate of 33% in the placebo group. The remission rates were also significantly better in patients receiving venlafaxine ER compared with those receiving placebo (31% and 16%, respectively).

Whether there is a clear dose-response relationship with venlafaxine ER in treating social anxiety disorder remains uncertain. Only 1 study has examined 2 or more fixed doses of venlafaxine ER (75 mg/day vs. 150–225 mg/day) in patients with social anxiety disorder. Although both doses were more efficacious than placebo, there was no evidence of a significant dose-response effect.[31]

Panic disorder. Results of studies of patients with panic disorder have suggested that cognitive-behavioral therapy and pharmacologic agents, such as TCAs, benzodiazepines, SSRIs, the TCA desipramine, and the NRI reboxetine, are effective in relieving patients' symptoms.[38,42–47,58,59]

Results of open-label studies of desipramine suggest its efficacy in treating panic disorder. A study of cocaine-related panic attacks[42] assessed the efficacy of low-dose desipramine (initial doses of 2.5 to 10 mg/day, slowly increased to an average daily dose of 25 mg) in 13 patients meeting DSM-III-R criteria for panic disorder that started during or shortly after cocaine exposure. This treatment strategy produced almost full resolution of panic attacks among 11 patients who were able to tolerate an initial increase in panic anxiety. In addition, a 6-week open trial[43] of desipramine (mean dose of 198 mg/day) in 15 patients with panic disorder found that 80% of the patients were globally rated as much or very much improved at endpoint.

The efficacy of desipramine in the treatment of panic disorder has been evaluated in 2 short-term double-blind studies. A 12-week study evaluated the efficacy of desipramine (N = 28) compared with placebo (N = 28) in patients with panic disorder with or without agoraphobia.[45] Desipramine-treated patients had significantly greater improvement compared with placebo recipients, as measured by HAM-A and global phobia ratings. There was a trend toward greater global improvement with desipramine, but no between-group differences on panic attack frequency

Table 3. Randomized, Double-Blind, Placebo-Controlled Studies of Venlafaxine Treatment of Panic Disorder

Study	Duration	Treatment Group, Daily Dose, (N)	Primary Outcome Measure	Results at Endpoint
Pollack et al, 2004[35]	12 wk	Venlafaxine ER 75 mg (N = 157) Venlafaxine ER 150 mg (N = 158) Paroxetine 40 mg (N = 160) Placebo (N = 154)	Percentage of patients free from full-symptom panic attacks	Venlafaxine ER 75 mg: 54% Venlafaxine ER 150 mg: 60% Paroxetine: 61% Placebo: 35% All $p < .001$ vs placebo
Whitaker et al, 2003[34]	10 wk	Venlafaxine ER 75–225 mg (N = 160) Placebo (N = 168)	Percentage of patients free from full-symptom panic attacks	Venlafaxine ER: 55% Placebo: 52% p = NS
Liebowitz et al, 2004[60]	10 wk	Venlafaxine ER 75–225 mg (N = 155) Placebo (N = 155)	Percentage of patients free from full-symptom panic attacks	Venlafaxine ER: 51% Placebo: 41% p = .056

Abbreviations: ER = extended release, NS = not significant.

were discerned. By week 12, 85% (22/26) of desipramine-treated patients were panic-free compared with 76% (13/17) of placebo-treated patients. A smaller 16-week study compared the efficacy of clomipramine with desipramine hydrochloride in 17 outpatients with panic disorder using a double-blind, crossover design.[47] Both active treatments led to significant improvement from baseline in panic attack frequency and behavioral ratings ($p < .001$); however, clomipramine led to a greater reduction in the frequency of panic attacks ($p = .028$) and was superior to desipramine on several ratings of anxiety (NIMH Global Anxiety, Zung Anxiety Scale [Raw and Index], and Spielberger Anxiety Scale). Although clomipramine appeared to be more effective, both drugs appeared to have significant therapeutic effects.

The results of 3 short-term studies are available to assess the possible efficacy of the SNRI venlafaxine ER in treating panic disorder (Table 3).[34,35,60] In one short-term study, administration of venlafaxine ER in flexible doses ranging from 75 to 225 mg/day (N = 160) or placebo (N = 168) was given.[34] Venlafaxine ER was significantly more efficacious than placebo in terms of the response rate and the remission rate ($p < .05$). In a second short-term study,[60] the primary outcome measure (the percentage of patients free from full-symptom panic attacks) was not significantly different at the end of treatment at 10 weeks, although it approached significance ($p = .056$). Additionally, venlafaxine ER treatment resulted in significant improvements over placebo on 8 of 13 secondary outcome measures, including the Panic Disorder Severity Scale (PDSS) total score, response rates (CGI-I = 1 or 2), and remission rates (CGI-I = 1 and panic free). The third study[35] compared treatment with venlafaxine ER in 1 of 2 fixed doses: 75 mg (N = 157) or 150 mg (N = 158) with paroxetine (40 mg/day; N = 160) or placebo (N = 154) (Table 3). Based on the primary outcome of percentage of patients free from full-symptom panic attacks, the efficacy of venlafaxine for both doses was significantly better than placebo beginning at week 4, through the end of treatment at 12 weeks. Both the response rates and remission rates were also significantly greater with venlafaxine ER than with placebo. The response rates for venlafaxine ER 75 mg/day and 150 mg/day and placebo were 77%, 79%, and 56%, respectively ($p < .001$). The corresponding remission rates were 45%, 47%, and 27% ($p \leq .001$). None of the outcome measures showed significant differences between the venlafaxine ER doses or between venlafaxine ER and paroxetine. In the future, fixed-dose studies may help clarify if there is a dose-response relationship for venlafaxine in symptomological treatment of panic disorder.

Posttraumatic stress disorder. Serotonergic antidepressants have been used effectively in the treatment of PTSD. For example, double-blind, placebo-controlled studies have shown that sertraline is effective for short-term and long-term treatment, including prevention of relapse.[61,62] There is also evidence supporting the efficacy of paroxetine in short-term treatment of PTSD.[63–65]

Although there is evidence to support the efficacy of desipramine in the treatment of other anxiety states, its efficacy in PTSD has not been extensively investigated and remains questionable. A small (N = 18) 4-week double-blind crossover study comparing desipramine treatment (200 mg/day) with placebo in male U.S. veterans meeting DSM-III criteria for PTSD[46] found no changes in anxiety and other PTSD symptoms with desipramine compared with placebo, although there appeared to be some improvement in symptoms of depression.

An open-label study in combat veterans suggested that venlafaxine ER may have some clinical utility in this disorder.[66] More recently, a randomized, double-blind, placebo-controlled short-term study found significant improvements in venlafaxine ER–treated patients.[67] In this study, patients were given placebo (N = 179), venlafaxine ER (flexible doses of 37.5–300 mg/day; N = 179), or sertraline (25–200 mg/day; N = 173). The mean total daily doses were 164 mg for venlafaxine ER and 110 mg for sertraline; the mean maximum daily doses were 225 mg for venlafaxine ER and 151 mg for sertraline. Beginning as early as week 2, through the end of treatment at 12 weeks, venlafaxine ER was significantly more efficacious than

placebo in relief of PTSD symptoms. Rates of remission (defined as 17-item Clinician Administered PTSD Scale [CAPS-SX_{17}] score ≤ 20) were 30%, 24%, and 20% for venlafaxine ER, sertraline, and placebo, respectively, at week 12 (p = .02 venlafaxine ER vs. placebo). Remission rates associated with venlafaxine ER treatment were significantly greater than those with placebo at weeks 4, 6, and 12; there were no significant differences between sertraline and placebo remission rates at any timepoint. Finally, although the study was not powered to determine treatment superiority, it is of interest that remission rates were significantly greater with venlafaxine ER treatment than with sertraline treatment at weeks 4 and 6.

Obsessive-compulsive disorder. In a 12-week double-blind comparison of venlafaxine (doses up to 300 mg/day) and paroxetine (doses up to 60 mg/day), patients with OCD responded equally well to both medications.[37] Also, in a short-term single-blind trial, venlafaxine had efficacy comparable to clomipramine, based on a comparison of response rates.[68]

In a retrospective, open-label study,[69] 39 patients with OCD, including 29 who were resistant to prior treatment with SSRIs or clomipramine, were treated with flexible-dose venlafaxine (37.5–375 mg/day). Of the total population, 27 patients (69%) were sustained responders, including 22 of the 29 initial treatment-resistant patients.[69] However, results of a small-scale double-blind crossover study comparing venlafaxine and paroxetine found that, in patients who failed to respond to the initially assigned treatment, those who were switched to paroxetine responded more favorably than those switched to venlafaxine.[70] Therefore, further investigation will be necessary to determine the possible role of SNRIs in the treatment of OCD.

Treatment of Concomitant Depression and Anxiety

Approximately two thirds of patients with MDD have GAD or some degree of anxiety.[71] Therefore, antidepressants that effectively treat both depression and anxiety symptoms provide a useful therapeutic option.

A double-blind 4-week study compared the therapeutic effects of desipramine (median daily dose of 150 mg) and diazepam (median daily dose of 20 mg) on symptoms of depression and anxiety in 53 psychoneurotic outpatients with moderate-to-severe depression and anxiety.[44] Efficacy variables were derived from the Hamilton Rating Scale for Depression (HAM-D), HAM-A, and 2 clinical global impressions. Desipramine-treated patients scored significantly better than diazepam-treated patients on 26 of 51 variables, while diazepam-treated patients scored significantly better on 1 item pertaining to sleep.

An open-label study examined the efficacy of 8 weeks of venlafaxine treatment in outpatients diagnosed with MDD or dysthymia, in addition to GAD, and found venlafaxine led to a statistically significant response in depression symptoms in MDD patients after 8 weeks.[72] Additional studies in patients with MDD and anxiety symptoms have also reported significant improvements with venlafaxine treatment (Table 4). In a double-blind RCT, patients with MDD with anxiety symptoms were treated with venlafaxine ER (75–225 mg/day; N = 122), fluoxetine (20–60 mg/day; N = 119), or placebo for 12 weeks; efficacy was measured by the HAM-D and HAM-A total scores.[28] Overall, venlafaxine produced significantly better results than placebo, beginning at week 2, through the end of the study, as did fluoxetine. However, venlafaxine resulted in significant improvements in anxiety, compared with placebo, earlier than fluoxetine. Also, on the HAM-D depressed mood item, venlafaxine treatment, but not fluoxetine, was significantly better than placebo at week 2. The response rates for venlafaxine and fluoxetine were significantly better than placebo (67%, 62%, and 43%, respectively, p < .05).

A post hoc analysis of these data[27] evaluated the efficacy of venlafaxine ER (75–225 mg/day; N = 32), fluoxetine 20 to 60 mg (N = 33), and placebo (N = 25) in the subgroup of patients diagnosed with MDD and GAD. Venlafaxine treatment was found to be superior to placebo and superior to fluoxetine on the majority of measures (Table 4).[27] Again, the primary outcome measures were the HAM-D, HAM-A, and CGI scales. At the final assessment, patients with GAD and MDD who were treated with venlafaxine had significantly larger decreases in HAM-D and HAM-A scores than those treated with placebo, while fluoxetine-treated patients did not show significantly greater decreases compared with the placebo group.

In another double-blind 12-week study of patients with moderate depression and anxiety, patients were given venlafaxine (75–150 mg/day; N = 64) or fluoxetine (20–40 mg/day; N = 67).[26] The primary outcome measures were HAM-D total score, Montgomery-Asberg Depression Rating Scale total score, and CGI-I score. As in the previous studies, venlafaxine treatment was significantly more efficacious than fluoxetine treatment in treating both depression and anxiety symptoms.

Three meta-analyses of secondary outcome measures of anxiety symptoms in prior RCTs of venlafaxine treatment of patients with MDD have also shown significant improvements earlier and greater than fluoxetine[73] and placebo.[29,74] A pooled analysis of individual data on 1454 outpatients with MDD in 5 previous RCTs was conducted to compare the improvements in depressive and anxious symptoms in patients treated with venlafaxine, fluoxetine, or placebo.[73] In terms of response rate, venlafaxine was statistically significantly superior to fluoxetine from week 3 through week 6. When remission rates were assessed, venlafaxine was significantly better than fluoxetine from week 2 through week 6. While fluoxetine did result in significant improvements over placebo, in many measures venlafaxine outcomes surpassed fluoxetine. Specifically,

Table 4. Randomized, Double-Blind Studies of Venlafaxine Treatment of Anxiety and Depression

Study	Population	Duration	Treatment Group, Daily Dose, (N)	Primary Outcome Measure(s)	Results
Silverstone and Ravindran, 1999[28]	MDD and concomitant anxiety	12 wk	Venlafaxine ER 75–225 mg (N = 122) Fluoxetine 20–60 mg (N = 119) Placebo (N = 118)	HAM-D HAM-A CGI-I	Venlafaxine ER, fluoxetine: Significantly greater improvement vs placebo on all outcome variables No significant differences between active treatment groups HAM-D: p < .001 venlafaxine ER vs placebo p < .001 fluoxetine vs placebo HAM-A: p < .01 venlafaxine ER vs placebo p < .05 fluoxetine vs placebo CGI-I: p < .001 venlafaxine ER vs placebo p < .001 fluoxetine vs placebo
Silverstone and Salinas, 2001[27]	Comorbid MDD and GAD	12 wk	Venlafaxine ER 75–225 mg (N = 32) Fluoxetine 20–60 mg (N = 33) Placebo (N = 25)	HAM-D HAM-A CGI-I	Venlafaxine ER: Significantly greater improvement vs placebo on 2 of 3 variables (HAM-D, HAM-A) Fluoxetine: No significant differences vs placebo No significant differences between active treatment groups HAM-D: p < .05 venlafaxine ER vs placebo p = NS fluoxetine vs placebo HAM-A: p < .05 venlafaxine ER vs placebo p = NS fluoxetine vs placebo CGI-I: p = NS venlafaxine ER vs placebo p = NS fluoxetine vs placebo
De Nayer et al, 2002[26]	Depression and anxiety	12 wk	Venlafaxine 75–150 mg (N = 64) Fluoxetine 20–40 mg (N = 67)	HAM-D total score MADRS total score CGI-I	Significantly greater improvement with venlafaxine vs fluoxetine on 2 of 3 variables (HAM-D and MADRS) HAM-D: p = .0048 venlafaxine vs fluoxetine MADRS: p = .0035 venlafaxine vs fluoxetine CGI-I: p = .073 venlafaxine vs fluoxetine

Abbreviations: CGI-I = Clinical Global Impressions-Improvement, ER = extended release, GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, NS = not significant.

venlafaxine was significantly better than fluoxetine in treating psychic anxiety symptoms, beginning at week 1. MDD patients with severe anxiety (HAM-D psychic anxiety score > 2) had significantly higher remission rates when treated with venlafaxine beginning at week 3 until the end of the study, compared with placebo. Similar remission rate improvements were seen in moderately anxious MDD patients from weeks 4 through 6.

The SNRI duloxetine has also been found to be superior to placebo and/or SSRIs in the treatment of anxiety symptoms.[39] Symptoms of anxiety associated with depression were evaluated as secondary outcomes in several clinical trials. The anxiety data were derived from 4 short-term studies that measured HAM-D anxiety/somatization factor scores, HAM-D item 10 anxiety-psychic score, and HAM-A scores.[39] Two of the 4 studies were placebo-controlled, while 1 compared duloxetine with paroxetine and placebo, and 1 compared duloxetine with fluoxetine and placebo. As seen with venlafaxine, duloxetine (≥ 60 mg/day) relieved symptoms of anxiety based on several efficacy measures, was associated with significant improvements over placebo (on 8 of 10 measures), and was significantly better than fluoxetine or paroxetine (on 3 of 6 measures).[39]

Taken together this evidence is suggestive that dual-action drugs may have improved clinical efficacy in patients with mixed depression and anxiety.[75]

Tolerability of SNRIs in Treatment of Anxiety

Venlafaxine and duloxetine are generally well tolerated in patients with anxiety disorders and compare favorably with SSRIs. The tolerability profile of duloxetine is similar to that for venlafaxine. Overall, the tolerability profile for the use of venlafaxine in patients with anxiety disor-

ders is the same as that seen in patients with depression. Interestingly, both short-term treatment and long-term treatment are associated with similar initial rates of adverse events that decline over time. For both depression and anxiety treatment populations, the first week tends to be associated with a higher rate of side effects.[28,76–78]

One of the most common adverse events associated with SNRIs is nausea, followed by headache, dizziness, somnolence, and dry mouth,[28,76–80] all of which are also associated with SSRI treatment. Venlafaxine- or duloxetine-related nausea generally occurs more frequently at higher doses and tends to resolve within 2 weeks.[28,76–78,81] Like the SSRIs, the SNRIs also may be associated with sexual dysfunction.[79,80] The incidence of sexual dysfunction associated with SNRIs is generally comparable to that of SSRIs[82,83]; however, there is some evidence to suggest a lower likelihood of sexual adverse events with duloxetine compared with some SSRIs.[84,85] Unlike SSRI treatment, treatment with venlafaxine or duloxetine may be associated with elevated blood pressure in some patients.[79,80] Finally, it is worth noting that, although SNRIs might be expected to exacerbate symptoms of anxiety due to their noradrenergic effects, the overall evidence from studies of SNRIs in patients with depression and/or anxiety disorders suggests that this is not the case.

CONCLUSIONS

There is some clinical evidence that drugs that alter norepinephrine neurotransmission (such as desipramine) are as clinically effective in the treatment of anxiety disorder as drugs that alter serotonergic neurotransmission. Thus, it is not surprising that SNRIs appear to be effective in the treatment of anxiety disorders and anxiety associated with depression. At present, the majority of the data concerns venlafaxine, which has been investigated in primary anxiety disorders as well as comorbid anxiety and depression. Preliminary data suggest that duloxetine is effective in the treatment of anxiety symptoms associated with depression, but no clinical trials are currently available that have evaluated the efficacy of duloxetine treatment in patients with primary anxiety disorders. A third SNRI, milnacipran, has been investigated only in the treatment of major depression.

Numerous studies show that venlafaxine has equal or greater efficacy than SSRIs in treating anxiety disorders, with comparable tolerability. There are currently no head-to-head studies comparing the efficacy of SNRIs and SSRIs in the treatment of GAD. There are, however, 2 large-scale RCTs that have found venlafaxine ER to be similar in efficacy to paroxetine in the treatment of social anxiety disorder.[30,32] There is also some suggestion that venlafaxine ER may offer an advantage over SSRIs in treating panic disorder and PTSD,[35,67] although additional studies will be needed to confirm these initial findings. Further, SNRIs may have an advantage over SSRIs in resolving the symptoms of comorbid anxiety and depression and bringing patients to remission.[26–28] Specifically, in recent RCTs, venlafaxine was found to be significantly better than fluoxetine, with significant improvement beginning sooner with venlafaxine than with fluoxetine.

Tolerability issues can outweigh the therapeutic benefits of antidepressant treatment. While excessive sedation, physical dependency, and withdrawal effects associated with TCAs and benzodiazepines often limit their use, the side effect profiles of SNRIs are generally comparable to those of SSRIs. Most of the tolerability data for SNRIs, particularly in terms of direct comparisons to SSRIs, have been derived from studies of treatment of major depression. Nevertheless, the tolerability of SNRIs in patients with primary anxiety disorders and comorbid anxiety and depression is comparable to what has been observed in depressed patients, with no evidence of anxiogenic effects.

Venlafaxine and duloxetine appear to be at least as effective as SSRIs in the treatment of anxiety disorders and symptoms of anxiety, with comparable tolerability. An important question that remains to be confirmed with future studies is whether large well-controlled studies of drugs that act exclusively on norepinephrine neurotransmission will find them to be equally effective in the treatment of anxiety as SSRIs. Also, it will be important to determine if combined actions on norepinephrine and serotonin provide a clinical advantage over pharmacologic activation of either neurotransmitter system alone, as is now suggested by some studies in PTSD, social anxiety disorder, panic disorder, and mixed depression and anxiety.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), diazepam (Valium and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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