The Patient With Comorbid Depression and Anxiety: The Unmet Need

David Bakish, M.D., F.R.C.P.C.

Major depression and anxiety occur concomitantly in general practice, occur in more patients than either depression or anxiety alone, and are associated with significant morbidity. When depression and anxiety occur together, they are associated with more severe symptoms, increased impairment, a more chronic course and poorer outcome, and a higher incidence of suicide. As many as 80% of patients with generalized anxiety disorder (GAD) have symptoms of depression. Patients with depression and comorbid anxiety present special treatment challenges with selection of drugs that have demonstrated efficacy for both depression and anxiety. A range of effective pharmacotherapeutic strategies are available, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, the 5-HT_2 blocker nefazodone, and the serotonin-norepinephrine reuptake inhibitor venlafaxine. Venlafaxine has been extensively evaluated for the treatment of depression and symptoms of anxiety in post hoc analyses. The efficacy of venlafaxine extended release (XR) has been demonstrated in patients with depression and concomitant anxiety. Further, venlafaxine XR is the first antidepressant that has demonstrated significant pure anxiolytic effects in prospective clinical trials of patients with GAD. The spectrum of pure depression, comorbid depression and anxiety disorders, and pure anxiety presents a treatment challenge. Venlafaxine offers a unique pharmacologic approach for the entire spectrum of these disorders.
(J Clin Psychiatry 1999;60[suppl 6]:20–24)

Major depression and anxiety occur concomitantly in general practice, occur in more patients than either depression or anxiety alone, and are associated with significant morbidity.[1,2] Patients with depression and anxiety represent more than 10% of psychiatric illness treated by primary care physicians.[3] When depression and anxiety occur together, they are associated with more severe symptoms, increased impairment, a more chronic course and poorer outcome, and a higher incidence of suicide.[4] Anxiety is a significant predictor of suicide in patients with major depression,[2,5] and attempted suicide is more common among patients with mixed anxiety-depressive disorders (up to 30%) than those with depression alone (approximately 10%).[6]

Among patients with generalized anxiety disorder (GAD), it has been reported that the majority have depressive symptoms and the lifetime prevalence of major depression is over 50%.[7] Due to the high prevalence of unipolar depression and GAD and to the overlap of symptoms between the 2 conditions, the occurrence of comorbid depression and GAD is the most common psychiatric condition.[7] Regardless of the type of anxiety disorder, patients with depression and anxiety often are underrecognized and undertreated. It is clear that patients with depression and comorbid anxiety disorders require selection and implementation of effective long-term pharmacotherapy.

MANAGEMENT OF DEPRESSION AND COMORBID ANXIETY

Patients with comorbid depression and anxiety present special treatment challenges. Depression is usually the primary target of treatment interventions, but medications should be selected that have demonstrated efficacy for both depression and anxiety. A range of effective pharmacotherapeutic strategies are available, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), 5-HT_2 blockers, and newer agents such as venlafaxine.

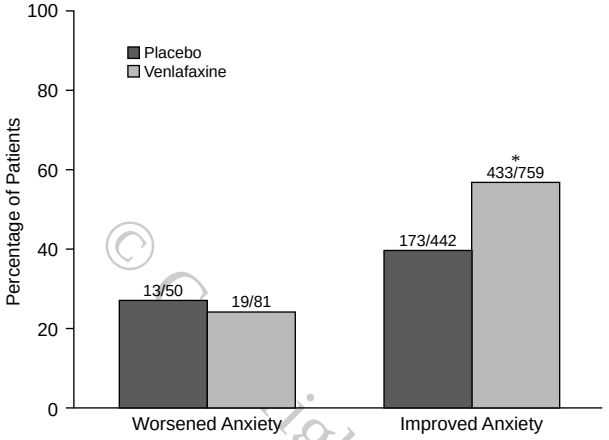
Depression with anxiety symptoms and a variety of anxiety disorders including panic disorder, social phobia, obsessive-compulsive disorder, and GAD have been treated with SSRIs.[8] Placebo-controlled trials of fluoxetine, fluvoxamine, paroxetine, and sertraline, as well as

From the Department of Psychiatry, Psychopharmacology Unit, Royal Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada.

Presented at the satellite symposium "Goal of Antidepressant Therapy: Response or Remission and Recovery?" which was held at the 21st Collegium Internationale Neuropsychopharmacologicum Congress, July 14, 1998, in Glasgow, Scotland, and supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories.

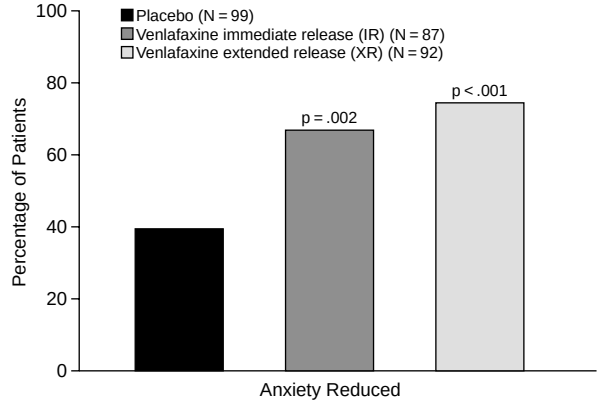
Reprint requests to: David Bakish, M.D., F.R.C.P.C., Psychopharmacology Unit, Royal Ottawa Hospital, University of Ottawa, 1145 Carling Ave., Room 1005A, Ottawa, Ontario, CANADA K1Z 7K4.

Figure 1. Proportion of Patients With a Change From Baseline in Hamilton Rating Scale for Depression Psychic Anxiety Item Score[a]



[a]Adapted from reference 14, with permission.
*p ≤ .001 vs. placebo.

Figure 2. Proportion of Patients With a Reduction in Anxiety From Baseline to Final On-Therapy Evaluation[a]



[a]Adapted from reference 15, with permission. Baseline HAM-D psychic anxiety item score of ≥ 2 and a final on-therapy score of < 2.
p Value vs. placebo.

nefazodone, have shown efficacy for the treatment of patients with depression and symptoms of anxiety or comorbid depression and anxiety.[9–13] However, none of these agents has been shown to be effective for the treatment of anxiety alone.

Venlafaxine has been extensively evaluated for the treatment of depression and symptoms of anxiety in post hoc analyses.[14,15] Results from prospective studies document the efficacy of venlafaxine in patients with depression and concomitant anxiety and, most recently, in those with GAD.[16–19]

VENLAFAXINE IN PATIENTS WITH DEPRESSION AND ANXIETY

Venlafaxine has undergone extensive retrospective and prospective clinical evaluation among patients with anxiety disorders. Evidence of the beneficial effects of venlafaxine in patients with depression and symptoms of anxiety was noted in a placebo-controlled study versus imipramine in general practice patients.[20] The effect of venlafaxine on anxiety symptoms in depressed patients was examined in a meta-analysis of pooled data from 6 short-term, placebo-controlled trials.[14] Anxiety was assessed from the Hamilton Rating Scale for Depression (HAM-D) psychic anxiety item scores and the HAM-D anxiety-somatization factor. Depressed patients with anxiety at baseline had significant ($p < .01$) improvement with venlafaxine by week 3 for the anxiety-somatization factor. Venlafaxine was significantly effective in reducing mean scores for the HAM-D psychic anxiety item and in alleviating symptoms of anxiety as early as week 1 (Figure 1).

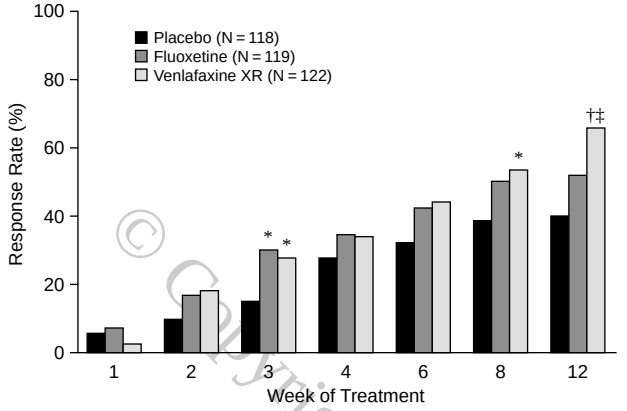
A cohort of patients with anxiety symptoms and major depression was examined from 2 double-blind, placebo-controlled studies of venlafaxine extended release (XR).[15] Among patients with at least moderate anxiety before the study, a significant reduction ($p \leq .01$ to $p < .001$) in HAM-D psychic anxiety item scores was noted with venlafaxine XR as early as week 4. A higher proportion of patients taking venlafaxine XR had a reduction in anxiety during treatment (Figure 2).

A prospective, 12-week, randomized, double-blind, placebo-controlled study compared once-daily venlafaxine XR and fluoxetine in 359 patients with major depression and concomitant anxiety.[16] In this study, patients were specifically required to have symptoms of anxiety at baseline to be eligible for the study. Patients received venlafaxine XR 75 mg once daily or fluoxetine 20 mg once daily initially, but the dose could be increased to venlafaxine XR, 150 to 225 mg/day, or fluoxetine, 40 to 60 mg/day. Both venlafaxine XR and fluoxetine were superior ($p < .05$) to placebo by week 2 on the HAM-D and maintained superiority to the end of the study. However, the response rate on the Hamilton Rating Scale for Anxiety (HAM-A) at week 12 was significantly ($p < .05$) higher with venlafaxine XR (65%) than with fluoxetine (51%) and placebo (39%) (Figure 3). These findings show that once-daily venlafaxine XR may be more effective than fluoxetine for patients with major depression and concomitant anxiety. This is an important finding since patients with depression and concomitant anxiety are often less responsive to treatment than patients with major depression alone.

GENERALIZED ANXIETY DISORDER

Generalized anxiety disorder is characterized by excessive worry and apprehension with psychic and somatic complaints of anxiety and stress. The diagnostic classification of GAD has evolved over the past 2 decades from a

Figure 3. Response Rate (≥ 50% decrease from baseline) on the Hamilton Rating Scale for Anxiety (HAM-A) With Placebo, Fluoxetine, or Venlafaxine XR[a]



[a]Adapted from reference 16, with permission.
*p < .05 vs. placebo.
†p < .001 vs. placebo.
‡p < .05 vs. fluoxetine.

disorder that was grouped with other mood disorders to an independent classification that includes symptoms to discriminate between normal and pathological anxiety. In the United States, the 1-year prevalence of GAD in the general population is about 3%, with a lifetime prevalence ranging from 4.0% to 6.6%.[7,21] Over 90% of patients with GAD have concomitant anxiety disorders, and over 50% have some depressive disorder.[7] Up to 15% of patients with GAD may attempt suicide.

Benzodiazepines, buspirone, and TCAs have been used to treat GAD. Benzodiazepines, like diazepam, alprazolam, and lorazepam, are effective short-term for relieving symptoms of anxiety.[8] However, long-term use of benzodiazepines carries with it withdrawal and dependence potential and potentially significant drug-drug interactions. Benzodiazepines usually are recommended for early, short-term treatment of patients with mixed anxiety and depression or depression with symptoms of anxiety, while awaiting a response to more effective drugs.[8]

The most rigorous study of TCAs among patients with GAD was a placebo-controlled comparison of imipramine, trazodone, and diazepam.[22] Diazepam was more effective during the first 2 weeks of treatment for relief of somatic symptoms of GAD; however, the antidepressants, especially imipramine, were more effective than diazepam on psychic anxiety symptoms beginning at week 3.

Buspirone, a nonbenzodiazepine anxiolytic, is the only product other than benzodiazepines approved for the treatment of GAD. Controlled clinical trials have demonstrated the efficacy of buspirone for GAD diagnosed by DSM-III criteria.[23–25] While buspirone is most effective against psychic symptoms of GAD and has no apparent drug interactions with other CNS drugs, the routine use of buspirone may be limited by a slow onset of action.[26] Also, questions remain about the efficacy of buspirone in patients with depression and comorbid GAD.

The placebo-controlled comparison of imipramine, trazodone, and diazepam found a more rapid onset of response with diazepam, but greater reduction in symptoms with imipramine, while trazodone was intermediate.[22] Disadvantages of TCAs are a delayed onset of activity and common side effects like daytime sedation and anticholinergic effects.[8,27] SSRIs have undergone limited investigation for the treatment of GAD.[8] An open-label study of paroxetine, imipramine, and a benzodiazepine found that paroxetine and imipramine were superior to the benzodiazepine for relief of psychic anxiety symptoms by the fourth week of treatment.[28] A preliminary, open-label study of venlafaxine in 9 patients with GAD noted a response in 5 patients after 4 weeks of treatment and provided support for the development of a comprehensive clinical trials program with venlafaxine XR for GAD.[29]

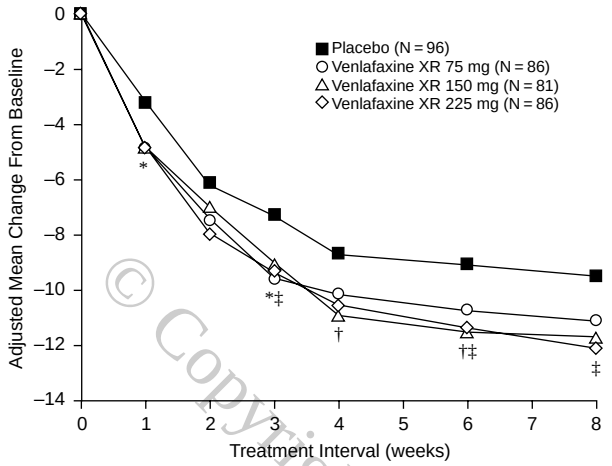
A series of double-blind, randomized, placebo-controlled trials were then conducted to evaluate the efficacy and tolerability of venlafaxine XR in patients satisfying DSM-IV criteria for GAD.[17–19] Each trial used similar enrollment criteria, which included outpatients satisfying DSM-IV criteria for GAD who had symptoms necessitating anxiolytic therapy, a minimum score of 18 on the HAM-A total and scores of ≥ 2 on item 1 (anxious mood) and item 2 (tension), a Covi Anxiety Scale score higher than a Raskin Depression Scale score, and a Raskin score ≤ 9. These trials were specifically designed to exclude patients with DSM-IV major depression. Efficacy in all trials was assessed from the HAM-A total score and psychic and somatic items, Clinical Global Impressions (CGI) score, Hospital Anxiety and Depression scale anxiety factor, and the Covi-Raskin score.

A randomized, placebo-controlled, parallel-group, dose-finding study was conducted in outpatients with GAD.[17] Patients were treated with venlafaxine XR 75 mg, 150 mg, or 225 mg/day for 8 weeks. Significant reductions from placebo were observed with venlafaxine XR on the HAM-A scale beginning as early as week 1 and continuing at weeks 3, 4, 6, and 8 (Figure 4). Similar reductions were observed for the HAM-A psychic anxiety factor scores.

An 8-week study compared the efficacy and tolerability of once-daily venlafaxine XR and buspirone in 365 outpatients with GAD.[18] Patients received fixed doses of venlafaxine XR 75 or 150 mg/day or buspirone 30 mg/day. Venlafaxine XR 75 and 150 mg were superior to placebo on the HAM-A psychic anxiety (Figure 5), anxious mood, and tension items and the CGI-Improvement scale, and superior to buspirone on the anxious mood item and Hospital Anxiety and Depression scale (Figure 6). Buspirone showed no significant advantages over placebo or venlafaxine XR at any time point.

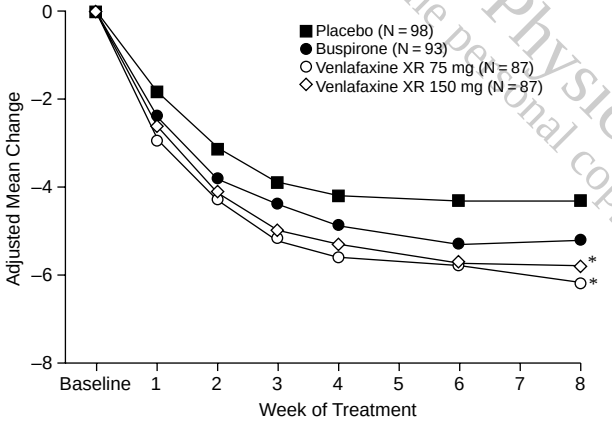
A 6-month, flexible-dose trial evaluated venlafaxine XR 75 to 225 mg/day versus placebo in 238 patients with

Figure 4. Mean Change From Baseline in HAM-A Total Score[a]



[a]From reference 17, with permission.
*p ≤ .05 for 75 mg, † for 150 mg, and ‡ for 225 mg vs. placebo.

Figure 5. Mean Change From Baseline in HAM-A Psychic Anxiety Item Score[a]



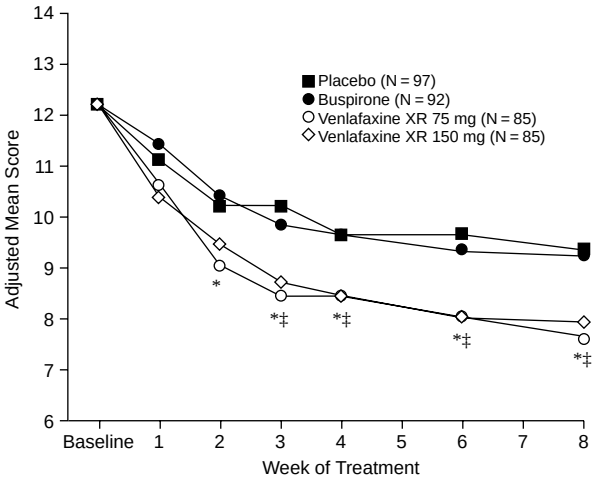
[a]Data from reference 18.
*p < .05 vs. placebo.

GAD.[19] Significant decreases were observed with venlafaxine XR on the HAM-A total and anxiety factors, Hospital Anxiety and Depression scale, CGI-Improvement scale, and Covi-Raskin scale beginning at week 1 and continuing to 6 months. The HAM-A response rate (≥ 50% reduction from baseline) reached 70% with venlafaxine XR by week 8 and was maintained at this level to the end of the study, while the placebo response rate was approximately 40% from week 8 to 28.

SUMMARY

The spectrum of pure depression, comorbid depression and anxiety disorders, and pure anxiety presents a treatment challenge. Effective treatment of comorbid depression and anxiety necessitates the use of drugs that have demonstrated efficacy for both conditions. Venlafaxine offers an alternative to antidepressants or other pharmacologic agents, potentially providing increased effectiveness and better tolerability.

Figure 6. Mean Hospital Anxiety and Depression Scale Scores[a]



[a]From reference 18, with permission.
*p < .05, venlafaxine XR 75 mg vs. placebo and buspirone.
‡p < .05, venlafaxine XR 150 mg vs. placebo and buspirone.

The diagnosis of GAD has evolved in recent years and with it the need for effective treatment. An extensive clinical trials program has demonstrated the effectiveness of venlafaxine XR for the treatment of patients with GAD, thereby serving as a model for evaluating the pure anxiolytic effects of venlafaxine. The success in GAD clinical trials differentiates venlafaxine among antidepressants as a proven and effective anxiolytic with efficacy across the depression-anxiety spectrum. Clinical data with venlafaxine support more widespread use for treatment of the spectrum of mood disorders that includes depression with or without anxiety and anxiety with or without depression.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

REFERENCES

1. Fawcett J, Kravitz HM. Anxiety syndromes and their relationship to depressive illness. J Clin Psychiatry 1983;44(8, sec 2):8–11
2. Fawcett J. Suicide risk factors in depressive disorders and in panic disorder. J Clin Psychiatry 1992;53(suppl 3):9–13
3. Regier DA, Boyd JH, Burke JD, et al. One-month prevalence of mental disorders in the US: based on five Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1988;45:977–986
4. Clayton PJ, Grove WM, Coryell W, et al. Follow-up and family study of anxious depression. Am J Psychiatry 1991;148:1512–1517
5. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
6. Vollrath M, Angst J. Outcome of panic and depression in a seven-year follow-up: results of the Zurich study. Acta Psychiatr Scand 1989;80:591–596

7. Wittchen HU, Zhao S, Kessler RC, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:355–364
8. Gorman JM. Comorbid depression and anxiety spectrum disorders. Depression Anxiety 1997;4:160–168
9. Beasley CM, Sayler ME, Bosomworth JC, et al. High-dose fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. J Clin Psychopharmacol 1991;11:166–174
10. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry 1992;53(suppl 2): 44–47
11. Kasper S, Moller H-J, Montgomery SA, et al. Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine and imipramine. Int Clin Psychopharmacol 1995;9 (suppl 4):3–12
12. Moon CAL, Jago W, Wood K, et al. A double-blind comparison of sertraline and clomipramine in the treatment of major depressive disorder and associated anxiety in general practice. J Psychopharmacol 1994;8:171–176
13. Zajecka JM. The effect of nefazodone on comorbid anxiety symptoms associated with depression: experience in family practice and psychiatric outpatient settings. J Clin Psychiatry 1996;57(suppl 2):10–14
14. Rudolph RL, Entsuah R, Chitra R. A meta-analysis of the effects of venlafaxine on anxiety associated with depression. J Clin Psychopharmacol 1998;18:136–144
15. Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. J Affect Disord 1998;47:50–58
16. Silverstone PH, Ravindran A, for the Venlafaxine XR 360 Canadian Study Group. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. J Clin Psychiatry 1999; 60:22–28
17. Haskins JT, Aguiar L, Pallay A, et al. for the Venlafaxine XR 210 Study Group. Double-blind, placebo-controlled study of once daily venlafaxine XR in outpatients with generalized anxiety disorder [abstract]. Presented at the 11th Congress of the European College of Neuropsychopharmacology; Oct 31–Nov 4, 1998; Paris, France
18. Haskins JT, Rudolph R, Aguiar L, et al. for the Venlafaxine XR 214 Study Group. Double-blind, placebo-/comparator-controlled study of once daily venlafaxine XR and buspirone in outpatients with generalized anxiety disorder [abstract]. Presented at the 11th Congress of the European College of Neuropsychopharmacology; Oct 31–Nov 4, 1998; Paris, France
19. Haskins JT, Rudolph R, Aguiar L, et al. for the Venlafaxine XR 218 Study Group. Venlafaxine XR is an efficacious short- and long-term treatment for generalized anxiety disorder [abstract]. Presented at the 11th Congress of the European College of Neuropsychopharmacology; Oct 31–Nov 4, 1998; Paris, France
20. Lecrubier Y, Moon CAL, Schifano F, et al. Efficacy of venlafaxine in depressive illness in general practice. Acta Psychiatr Scand 1997;95:485–493
21. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 1994;51:8–19
22. Rickels K, Downing R, Schweizer E. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993;50:884–895
23. Rickels K, Weisman K, Norstad N, et al. Buspirone and diazepam in anxiety: a controlled study. J Clin Psychiatry 1982;43(12, sec 2):81–86
24. Casacalenda N, Boulenger JP. Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications. Can J Psychiatry 1998;43:722–730
25. Feighner JP. Buspirone in the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 1987;48(suppl 12):3–6
26. Sussman N. How to manage anxious patients who are depressed. J Clin Psychiatry 1993;54(suppl 5):8–16
27. Nutt D. Management of patients with depression associated with anxiety symptoms. J Clin Psychiatry 1997;58(suppl 8):11–16
28. Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand 1997;95:444–450
29. Johnson MR, Emmanuel N, Crawford M, et al. Treatment of generalized anxiety disorder with venlafaxine: a series of 11 cases. J Clin Psychopharmacol 1998;18:418–419