Key Words: depression, anxiety, antidepressants, serotonin, tricyclic antidepressants, monoamine oxidase inhibitors, norepinephrine, SSRI, SNRI, venlafaxine, response, remission

Optimizing Treatment Outcomes for Patients With Depression and Generalized Anxiety Disorder

By Michael E. Thase, MD, and Madhukar Trivedi, MD

ABSTRACT *~The goal of the acute phase of pharmacotherapy of major depressive disorder or generalized anxiety disorder is remission (ie, complete resolution of symptoms) rather than simply a response (eg, at least a ≥50% improvement in symptoms). Despite treatment, incompletely remitted patients often have persistent social and/or functional impairment, and are particularly vulnerable to relapse. To optimize outcomes, it is important to continue to adjust and refine the treatment plan until there is resolution of residual depressive symptoms and normalization of social functioning. Thereafter, prophylactic therapy is indicated to lessen the risk of recurrence and/or chronicity. Contemporary treatment options include older medications such as tricyclic antidepressants, newer compounds, such as selective serotonin reuptake inhibitors, the serotonin and norepinephrine reuptake inhibitor, venlafaxine, and a number of other medications with novel mechanisms of action. Although it has been conventional to assume that all antidepressants are equally effective, evidence from a recent pooled analysis of data from eight double-blind, randomized, controlled clinical studies suggests that venlafaxine therapy may be associated with higher remission rates.* Psychopharmacology Bulletin. *2002;36(Suppl 2):93-102*

Introduction

Depression and generalized anxiety disorder (GAD) are major public health problems; at least one of every four people in the United States will require treatment for one of these disorders during their lifetime.[1] In addition, there is a high level of comorbidity between anxiety and depression, and the majority of patients with depression have also experienced a previous anxiety disorder.[2] The presence of a comorbid condition can complicate treatment and result in a poorer outcome for the patient. Depression and GAD are associated with significant impairment in social, occupational, and other functioning,[3-5] particularly among those with moder-

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ate to severe symptoms.[6] Although comorbid anxiety and depression is often responsive to antidepressant treatment, improvement appears to be slower[6] and less complete.[7]

Traditionally, the success of antidepressant therapy has been judged by the proportion of treated patients who achieve an arbitrarily defined level of symptom improvement, for example, a ≥50% reduction in the Hamilton Rating Scale for Depression (HAM-D).[8] However, more recently it has been recognized that remission (ie, the complete resolution of symptoms) should be the goal of the acute phase of treatment.[9] This is because residual depressive symptoms are associated with persistent impairment of work, social, and family relationships, as well as an increased risk of relapse.[10] Reducing the risk of relapse/recurrence by achieving full remission will, in itself, lead to substantial and longstanding improvements in social functioning and overall quality of life.

Treatments currently available for depression are reasonably effective when judged by response rates. It has been estimated that 90% of patients could eventually respond to a series of five therapies under optimal conditions.[11] However, more than half of these patients do not fully remit during the first 6–8 weeks of treatment.[12] The probability of remaining symptom-free is far greater in patients with no residual depressive symptoms; in one study, 76% of patients with residual symptoms relapsed over the next 10 months, compared with 25% of those who had fully remitted.[13] Similarly, in a long-term, prospective study, patients with residual or subthreshold depressive symptoms were found to have a significantly more severe and chronic future course of illness than those who were asymptomatic at the start of follow-up.[14]

There are several aspects of the care of depressed patients that can be addressed to help improve outcomes. First, factors that are associated with a greater risk of incomplete remission or subsequent risk of recurrence should be taken into consideration. The fundamental principle is that the initial phase of treatment should be focused on remission and tailored to specific patient needs. Nonresponsive patients should have their treatment plans revised accordingly, both in terms of alternate medications and/or psychotherapy. Until recently, antidepressant medications were presumed to be comparably effective, and decisions about first-choice options were largely based on issues such as cost, convenience, tolerability, and safety.[15]

Remission-Focused Treatment of Depression

The treatment of depression is usually divided into three distinct phases: acute, continuation, and maintenance. In the initial phase of acute treatment, the goal is to reduce and, if possible, resolve all symptoms

(HAM-D ≤7) of depression, and restore psychosocial functioning to the premorbid or normal state. Continuation treatment follows, taking place after symptoms have responded to acute therapy, with the aim of ensuring a period of sustained remission. The continuation phase typically lasts 6–9 months, after which a sustained remission can be called recovery. The maintenance treatment phase begins after the patient has recovered, and is a form of prophylaxis, aiming to prevent recurrence over years or even a lifetime.[1,16]

The ideal treatment for depression or GAD is one that is predictably and rapidly effective, acceptable to all patients, and has minimal adverse events. There are no such treatments! The major classes of treatment include medication, psychotherapy and, in the case of depression, electroconvulsive therapy (ECT). The risks and benefits of each option need to be considered as part of the treatment-planning process. Medication is the most common form of therapy chosen by physicians because most general practitioners can provide this treatment competently. Moreover, compared with tricyclic antidepressants (TCAs), the newer types of medications, typified by selective serotonin reuptake inhibitors (SSRIs), are much easier for primary care physicians to prescribe in therapeutic doses. Although adverse events do occur, they can often be managed by dose adjustment, and only about 10% of prescriptions are discontinued because of these effects.

Psychotherapy has the benefit that it does not cause somatic adverse events, and it is recommended as an alternative to medication for treatment of patients with mild-to-moderate major depressive disorder who prefer to approach their illness from an interpersonal or psychological perspective.[1] Combined treatment may be more beneficial for patients who have shown a partial response to either treatment alone,[17] or who have more severe and recurrent[18] or chronic[19] illness. ECT tends to be reserved for patients with severe depression, who either have not responded to other forms of treatment, or require a rapid relief of symptoms because of psychosis, incapacity, or pervasive suicidality. Although ECT is clearly the most effective treatment for severe and psychotic forms of depression, the expense, potential for cognitive adverse events, limited acceptability of this therapy, and high risk of subsequent relapse justify its fourth-line ranking.[1]

During the acute phase of pharmacotherapy, patients are typically monitored every 1–2 weeks to assess adherence, check adverse events, monitor symptom status, and provide advice and support. The initial medication trial should be given for at least 4–6 weeks, and the patient's response, including symptomatic and functional outcomes, evaluated after this time.[1] If a patient is responding well to treatment, acute therapy should be continued until complete remission, followed by continuation therapy of at least 4–9 months.[1] If patients have shown

some improvement, it may be appropriate to adjust the dose or add psychotherapy. If there has been no improvement in symptoms, despite giving a maximally tolerated dose of antidepressant, the drug therapy should be augmented or changed. Following augmentation of the treatment regimen, the patient should be monitored and reassessed after 6 weeks. If there is still no improvement after a total of 12 weeks, the treatment should be changed again.

A practical method of sequential therapies is detailed in the algorithm presented by Trivedi (Trivedi, pages 142-149). Options for antidepressant nonresponders include switching the patient to a different class of antidepressant, augmentation of current monotherapy, ECT, and combination therapies.[11] A systematic approach to treatment of resistant disease provides clinicians with guidance as to the appropriate therapy for patients at different stages. Nevertheless, the treatment options remain flexible and, in some circumstances, treatments typically recommended for a later stage may be the most appropriate earlier in the course of the illness. Thus, while algorithms are helpful as templates, they should be used in conjunction with clinical experience.

Factors Influencing Likelihood of Remission and Relapse

Therapy for depression can fail at different times in the treatment course: some patients will fail to respond to initial therapy, some will respond but not achieve full remission, and others will respond but relapse during subsequent months of continuation or maintenance phase therapy. There are several factors that may result in continuing symptoms in patients undergoing treatment for depression.

Factors associated with nonresponse include: patient nonadherence, incomplete diagnosis (eg, failure to recognize psychotic features or bipolarity), misdiagnosis (eg, failure to recognize hypothyroidism), and an inadequate dosage or duration of treatment.[11] An incomplete diagnosis can also result from an unrecognized medical illness or substance abuse, which is not uncommonly minimized.

The starting point to improved adherence is to anticipate that about one third of patients will not take their medication as prescribed.[20] Too often, busy physicians take a "don't ask, don't tell" approach to their patients' medication-taking habits. Frank discussion of medication adherence, exploration of the patient's reservations about treatment, and education about the disorder and what to expect during treatment are useful strategies.

Where treatment has led to some degree of response, but not complete remission, additional factors may be involved. A high initial symptom rating has been shown to slow the course of remission[13]; chronicity, concurrent axis I and II comorbidities,[8] and medical comorbidity may also reduce

the probability of remission observed at the end of the first 6–8 weeks of antidepressant therapy.

Even patients who achieve remission during the acute phase treatment for depression are at risk of relapse during pharmacotherapy, albeit at a much lower level than those who only achieve a response. A history of frequent and/or multiple episodes, "double depression" (ie, antecedent dysthymia), onset after age 60 years, poor symptom control during continuation therapy, and comorbid anxiety disorder or substance abuse all increase the probability of relapse and recurrence of depression.[21] Adherence to treatment conveys the greatest possible chance of benefit from prophylactic therapy.

Effectiveness of Current Therapies

As discussed previously, a number of classes of antidepressant therapies are used for treating patients with depression. Since the early 1990s, SSRIs have often been the most widely prescribed treatment chosen by psychiatrists and generalists alike. However, other agents (including bupropion, venlafaxine, nefazodone, and mirtazapine) are now also considered effective treatments,[22,23] along with more conventional antidepressants like the TCAs.

Until the early 1990s, TCAs were the standard of antidepressant pharmacotherapy worldwide. Although thought to work primarily as norepinephrine reuptake inhibitors, several TCAs (clomipramine and, at higher doses, amitriptyline and imipramine) also inhibit the reuptake of serotonin. There is no doubt that TCAs are effective antidepressant agents; a comprehensive meta-analysis of published studies found that 51.5% of outpatients and 50% of inpatients responded to TCA treatment—an improvement of 21.3% and 25.1%, respectively, compared with placebo.[1] However, the adverse-event profile of TCAs often limits their use and an overdose as small as 7–10 days' supply can be lethal. This is a major limitation for treatment of a disorder with a significant risk of suicide.

SSRIs have a much better day-to-day tolerability profile than TCAs. They also have the benefit of a much safer profile in overdose. In the Agency for Health Care Research and Quality meta-analysis, SSRIs were shown to produce a response in 47.4% of outpatients, compared with 20.1% of patients in the placebo group.[1] A recent study compared the effectiveness of three SSRIs (paroxetine, fluoxetine, and sertraline) to each other over a period of 9 months.[24] All three SSRIs demonstrated similar effectiveness in patients (N=573) when measuring depressive symptoms and multiple domains of health-related quality of life.

Monoamine oxidase inhibitors (MAOIs) are no longer widely prescribed, partly because they are associated with tolerability problems generally comparable to TCAs.[25] Moreover, during MAOI therapy, patients must

agree to follow dietary restrictions to lessen the risk of a hypertensive reaction. This so-called "cheese-effect" results from inhibition of monoamine oxidase enzyme in the gut, preventing degradation of the pressor amine tyramine, which, in turn, releases norepinephrine into the bloodstream.

Despite these problems, there is no doubt that the older MAOIs are effective. A total of 57.4% of outpatients and 52.7% of inpatients responded to MAOI therapy—an improvement of 30.9% and 18.4% respectively, compared with placebo.[1] Outside the US, a selective and reversible MAOI, moclobemide, is available. This medication does not necessitate dietary restrictions associated with the older MAOIs. However, there are widespread concerns about the efficacy of moclobemide therapy, especially at lower dosages.[26]

In 1994, the first selective serotonin and norepinephrine reuptake inhibitor (SNRI) was introduced—the immediate-release formulation of venlafaxine. From the outset there was evidence that the "dual-reuptake" mechanism of action might be associated with greater efficacy than fluoxetine, at least at dosages of 150 mg/day or higher.[27,28] However, it was not until the extended-release (XR) formulation of venlafaxine was introduced in 1997 that this medication was widely perceived as a first-line option.

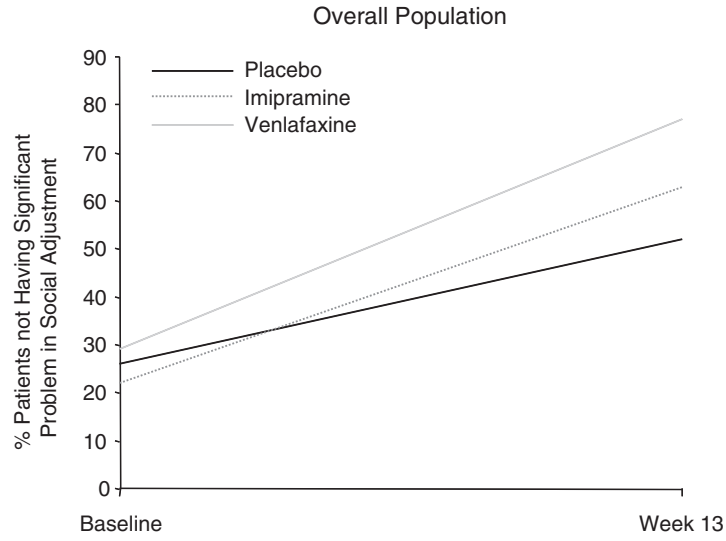
Evidence of the greater efficacy of venlafaxine has continued to grow, as illustrated by a pooled analysis of all original data from the first eight randomized, controlled clinical trials comparing the efficacy of venlafaxine or venlafaxine XR with SSRIs (fluoxetine, five studies; paroxetine, two studies; fluvoxamine, one study). A total of 2,045 patients with major depressive disorder were enrolled in these trials (Thase, pages 24–35).[29] Remission rates after 6–8 weeks of treatment were 45% for venlafaxine, 35% for SSRIs, and 25% for placebo. Venlafaxine was significantly more effective than the SSRIs from week 2, and versus placebo from week 3. SSRIs could be separated from placebo by week 4. Additional analyses of pooled data from a second wave of controlled studies are underway involving a greater number of SSRIs.

Improvements in psychosocial functioning following treatment with venlafaxine have also been demonstrated in patients with depression.[30] In a French study of patients recruited from general practice settings, an increase was observed in the proportion of those with no or minimal social impairment following 13 weeks of venlafaxine therapy (Figure 1A). Furthermore, the subgroup of patients with the most severe social impairment at baseline also showed significant improvements. In comparison, few patients in this subgroup improved when given placebo or imipramine (Figure 1B).

Although there are data from placebo-controlled studies demonstrating that venlafaxine is an effective treatment for GAD (Allgulander, pages 79–92),[31-34] no SSRI-controlled studies have so far been

FIGURE 1A

THE EFFECT OF VENLAFAXINE ON SOCIAL IMPAIRMENT IN PATIENTS WITH DEPRESSION



Adapted from: Lecrubier Y, Mahe V, Hackett D, Haudiquet V. Social adjustment of patients with depression is improved with effective treatment: a venlafaxine study in general practice. Poster presented at: Annual Meeting of the International Forum on Mood and Anxiety Disorders; 2000; Monte Carlo, PR.

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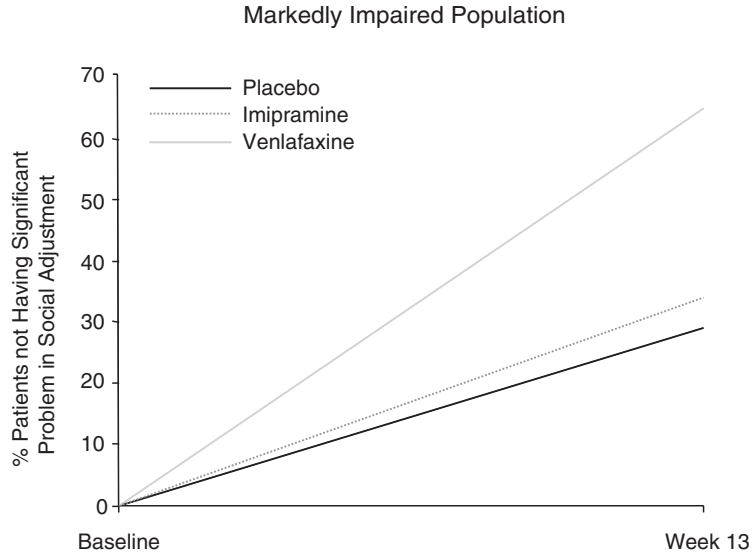
FIGURE 1B

THE EFFECT OF VENLAFAXINE ON SOCIAL IMPAIRMENT IN PATIENTS WITH DEPRESSION



Adapted from: Lecrubier Y, Mahe V, Hackett D, Haudiquet V. Social adjustment of patients with depression is improved with effective treatment: a venlafaxine study in general practice. Poster presented at: Annual Meeting of the International Forum on Mood and Anxiety Disorders; 2000; Monte Carlo, PR.

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completed. These studies will be critical to test whether a "dual reuptake" mechanism is an advantage (relative to a serotonin-selective mechanism of action) for GAD.

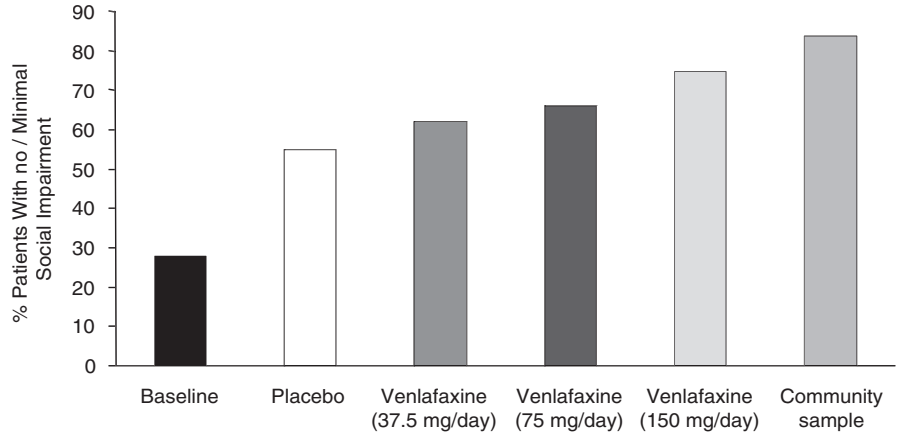
As with depression, the aims of acute treatment for GAD are to alleviate symptoms and return psychosocial functioning to a normal state. Venlafaxine therapy was shown to be associated with significantly improved psychosocial functioning in the placebo-controlled studies. For example, in a study of patients with GAD, 6 months of treatment with venlafaxine extended release (XR) at an appropriate dose reduced the proportion of patients with social impairment to levels similar to those seen in a general community sample (Figure 2).[35]

CONCLUSION

In recent years, the focus of treatment for depression has changed from achieving a response to aiming for full remission—ie, the resolution of symptoms of depression and a return to normal psychosocial functioning. This is due to the mounting evidence suggesting that patients who have some residual symptoms of depression and/or social impairment are more likely to relapse during the continuation phase of therapy or when treatment ceases. This change in emphasis has several implications for the treatment of depressed patients. Treatment should be continued, or new therapies or combinations should be tried, until the patient achieves full remission. Only at this point should a patient begin the continuation

FIGURE 2

THE EFFECT OF VENLAFAXINE ON SOCIAL IMPAIRMENT IN PATIENTS WITH GAD



GAD=generalized anxiety disorder.
Adapted from: Boyer P, Mahe V, Hackett D, Haudiquet V. Efficacy of venlafaxine ER in social adjustment in patients with generalized anxiety disorder. Poster presented at: Annual meeting of the European College of Neuropsychopharmacology; September 2000; Munich, Germany.

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phase of therapy. Continuation therapy usually comprises a treatment plan and visits to a physician, though less frequently than during the acute phase. Many patients require several treatment steps before treatment goals are met.

Like depression, GAD is a chronic and recurrent disorder. In the past, anxiety disorders were treated with benzodiazepines, but antidepressants have been used more recently. There are currently only two antidepressants that are indicated for GAD: paroxetine for short-term treatment (6–8 weeks) and venlafaxine for long-term treatment (up to 6 months). As with depression, the aim of GAD treatment is complete remission of symptoms. There are several factors that are known to predispose some patients to incomplete remission. In particular, severity, comorbidity, and chronicity have been shown to lower the probability of remission. Patients with these risk factors may need longer courses of treatment, combined therapy (ie, psychotherapy and pharmacotherapy) and sequential trials of different therapies before remission is achieved. The antidepressants that are currently recommended for use in depressed and anxious patients have traditionally been thought of as having comparable efficacy. However, the tolerability and safety profiles of TCAs and MAOIs have resulted in their infrequent use as first-line treatments. Antidepressants such as SSRIs and venlafaxine XR have at least similar response rates to TCAs, as well as more favorable adverse-event profiles and safety. The apparent advantage of venlafaxine's efficacy (relative to SSRIs) in highly controlled, randomized clinical trials must now be evaluated in everyday practice, including primary care. ✤

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DISCLOSURE

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REFERENCES

1. *Clinical Practice Guideline, Number 5: Depression in Primary Care, 2. Treatment of Major Depression*. Rockville, Md. US Department of Health and Human Services, Agency for the Health Care Policy and Research; 1993. AHCPR Publication Number 93-0551.
2. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of *DSM-III-R* major depressive disorder in the general population: Results from the US National Comorbidity Survey. *Br J Psychiatry*. 1996;30(suppl):17-30.

3. De Lisio G, Maremmani I, Perugi G, Cassano GB, Deltito J, Akiskal HS. Impairment of work and leisure in depressed outpatients. A preliminary communication. *J Affect Disord*. 1986;10:79-84.
4. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depress Anxiety*. 2000;12(suppl 1):69-76.
5. Roy-Byrne PP, Stang P, Wittchen H-U, Ustun B, Walters EE, Kessler RC. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. *Br J Psychiatry*. 2000;176:229-235.
6. Mintz J, Mintz LI, Arruda MJ, Hwang SS. Treatments of depression and the functional capacity to work. *Arch Gen Psychiatry*. 1992;49:761-768.
7. Bauwens F, Tracy A, Pardoen D, Vander Elst M, Mendlewicz J. Social adjustment of remitted bipolar and unipolar out-patients. A comparison with age- and sex-matched controls. *Br J Psychiatry*. 1991;159:239-244.
8. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-22.
9. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. *J Clin Psychiatry.* 1999;60(suppl 22):29-34.
10. Nierenberg AA, Wright EC. Evolution of remission as the new standard in the treatment of depression. *J Clin Psychiatry*. 1999;60(suppl 22):7-11.
11. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58(suppl 13):23-29.
12. Stahl SM. Why settle for silver, when you can go for gold? Response vs. recovery as the goal of antidepressant therapy. *J Clin Psychiatry*. 1999;60:213-214.
13. Paykel ES. Remission and residual symptomatology in major depression. *Psychopathology*. 1998;31:5-14.
14. Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry*. 2000;157:1501-1504.
15. Thase ME, Kupfer DJ. Recent developments in the pharmacotherapy of mood disorders. *J Consult Clin Psychol*. 1996;64:646-659.
16. Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry.* 1991;52(suppl):28-34.
17. Fava ME, Grandi S, Zielezny M, Canestrari R, Morphy MA. Cognitive behavioural treatment of residual symptoms in primary major depressive disorder. *Am J Psychiatry.* 1994;151:1295-1299.
18. Thase ME, Greenhouse JB, Frank E, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry*. 1997;54:1009-1015.
19. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioural-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Eng J Medicine*. 2000;342:1462-1470.
20. Kaplan EM. Antidepressant noncompliance as a factor in the discontinuation syndrome. *J Clin Psychiatry*. 1997;58:31-35.
21. Keller MB. Long-term treatment of depression. *J Clin Psychiatry.* 1999;60(suppl 17):41-45.
22. Kuzel RJ. Treating comorbid depression and anxiety. *J Fam Pract.* 1996;43(suppl 6):S45-S53.
23. Hirschfeld, RM. Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. *J Clin Psychiatry.* 1999;60:326-335.
24. Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care. A randomized trial. *JAMA*. 2001;286:2947-2955.
25. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology*. 1995;12:185-219.
26. Letufo-Neto F, Trivedi M, Thase ME. Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology*. 1999;20:226-247.
27. Clerc GE, Ruimy P, Verdeau-Palles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group. *Int Clin Psychopharmacol*. 1994;9:139-143.
28. Dierick M, Ravizza L, Realini R, Martin A. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Prog Neuro-Psychopharmacol Biol Psychiatry.* 1996;20:57-71.
29. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry.* 2001;178:234-241.
30. Lecrubier Y, Mahe V, Hackett D, Haudiquet V. Social adjustment of patients with depression is improved with effective treatment: a venlafaxine study in general practice. Poster presented at: Annual Meeting of the International Forum on Mood and Anxiety Disorders; 2000; Monte Carlo, PR.
31. Gelenberg AJ, Lydiard RB, Rudolph RL, Aguiar L, Haskins JT, Salinas E. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder. A 6-month randomized controlled trial. *JAMA*. 2000;283:3082-3088.
32. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *Am J Psychiatry*. 2000;157:968-974.
33. Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry.* 1999;60:528-535.
34. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (XR) in the treatment of generalized anxiety disorder: a 24-week placebo-controlled dose-ranging study. *Br J Psychiatry*. 2001;179:15-22.
35. Boyer P, Mahe V, Hackett D, Haudiquet V. Efficacy of venlafaxine ER in social adjustment in patients with generalized anxiety disorder. Poster presented at: Annual meeting of the European College of Neuropsychopharmacology; September 2000; Munich, Germany.