

The Pharmacoeconomics of Venlafaxine in Depression

Thomas J. Morrow, MD

Summary

The prevalence of depression and the high costs associated with its management have heightened interest in pharmacoeconomic evaluation of drug treatment, especially the use of selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor venlafaxine. A number of studies of venlafaxine in both inpatient and outpatient settings have revealed that extended-release venlafaxine has a lower expected cost than comparable treatment with SSRIs and tricyclic antidepressants (TCAs). When the relative cost effectiveness of immediate-release venlafaxine, SSRIs, and TCAs was assessed in the treatment of major depressive disorder in 10 countries, venlafaxine yielded a lower than expected cost compared with SSRIs and TCAs in all but 1 country. In comparing healthcare expenditures for depressed patients with and without anxiety, there was a pharmacoeconomic benefit to both immediate- or extended-release venlafaxine, regardless of the presence or absence of comorbid anxiety. A review of computerized administrative claims data from 9 US healthcare plans on resource use and the cost of venlafaxine instead of TCAs after switching from an SSRI showed that overall costs did not vary markedly between venlafaxine and TCAs. This led to the conclusion that although therapy with venlafaxine is more costly than TCA therapy, this increase may be offset by lower costs of other medical services. Such findings have enormous potential ramifications for practicing physicians in terms of venlafaxine's superior remission rate, lower likelihood of relapse, loss of fewer patients to adverse events or lack of efficacy, and flexibility in dosing that enables titration to achieve an optimal response.

Major depressive disorder (MDD) represents a significant public health problem that poses a substantial burden of illness to healthcare providers, payers, and patients. It has been projected that by 2020, depression will rank second in worldwide disease burden measured in disability-adjusted life years.¹ Even today, the economic burden of depression is staggering, with annual costs in the United States estimated to approach \$44 billion,² which is approximately equal to the cost of treating heart disease.³ (All dollar amounts in this report are quoted in US dollars.) Moreover, yearly direct treatment costs for depression in the United States, exclusive of medication acquisition costs, have been estimated at \$11.2 billion.⁴

As imposing as these estimates of the economic burden of depression appear, it is possible that they actually underestimate the true cost of depression because they take into account only the cost of treating *diagnosed* depression. Depression is not diagnosed in many patients,⁵ and the condition is inadequately treated in others.⁶ According to the World Health Organization, depression is estimated to be present in 10% of all patients seeking care at primary care facilities worldwide, but the condition is frequently unrecognized by primary care physicians.⁷ Therefore, the true economic burden of depression may be substantially greater than reported costs.

The prevalence of depression and the high costs associated with its manage-

ment have increased interest in pharmacoeconomic evaluations of drug treatment, particularly as the use of selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine has expanded.

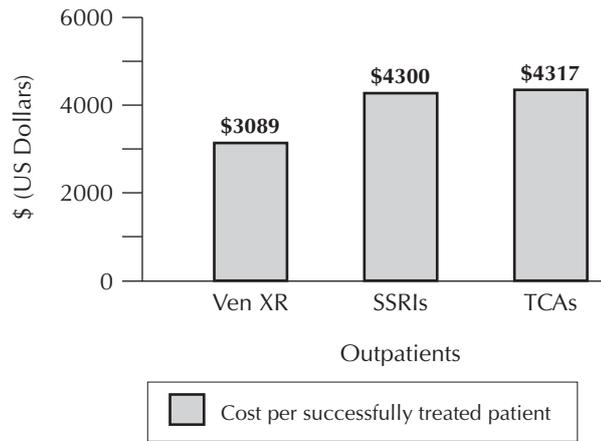
Impact of Venlafaxine Utilization Versus TCAs and SSRIs by Managed Care Organizations

To help facilitate formulary decisions by managed care organizations (MCOs), Casciano et al⁸ conducted a pharmacoeconomic analysis comparing the leading treatments for depression. The analysis involved a comparison of the tricyclic antidepressants (TCAs) amitriptyline, imipramine, desipramine, and nortriptyline; the SSRIs fluoxetine, sertraline, paroxetine, and fluvoxamine; and the SNRI venlafaxine. The objective was to quantify the impact of utilization of extended-release venlafaxine (venlafaxine XR) on both patients and payers. The authors performed a patient-level evaluation using a decision analytic model, and then applied the results to the policy level of the MCO to calculate the overall budgetary impact of increasing utilization of the most clinically effective therapy. The decision analytic model was derived using an expert panel, a meta-analysis of clinical trials, and a comprehensive valuation of healthcare resources relevant to depression treatment.

In the outpatient setting (Figure 1), venlafaxine XR provided a lower expected cost per patient (\$3089) compared with SSRIs (\$4300) and TCAs (\$4317). In the inpatient setting (Figure 2), the cost of treating a patient with depression with venlafaxine XR was estimated to be \$16,235. This figure represented a savings of \$1900 and \$1608 compared with SSRIs and TCAs, respectively.⁸

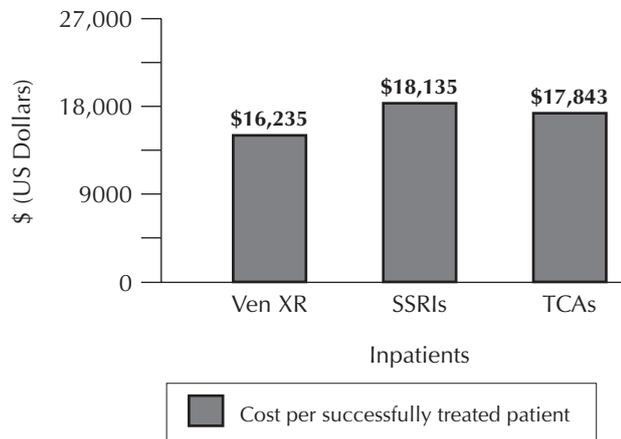
The authors estimated the direct cost of depression to a hypothetical 1 million-member health maintenance organization (HMO) to be approximately \$17 million, with the per-patient cost of treatment with venlafaxine XR estimated at \$4404 per episode, compared with an estimated current per-patient cost of

Figure 1. Pharmacoeconomic Comparison of Extended-Release Venlafaxine (Ven XR), Selective Serotonin Reuptake Inhibitors (SSRIs), and Tricyclic Antidepressants (TCAs) in Outpatients



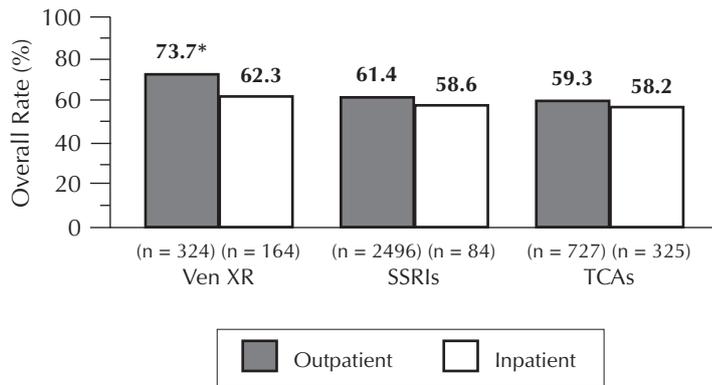
Source: Casciano R, Arikian SR, Tarride J-E, Casciano J, Doyle JJ. Antidepressant selection for major depressive disorder: The budgetary impact on managed care. *Drug Benefit Trends* 2000;12:6BH-17BH. Reprinted with permission.

Figure 2. Pharmacoeconomic Comparison of Extended-Release Venlafaxine (Ven XR), Selective Serotonin Reuptake Inhibitors (SSRIs), and Tricyclic Antidepressants (TCAs) in Inpatients



Source: Casciano R, Arikian SR, Tarride J-E, Casciano J, Doyle JJ. Antidepressant selection for major depressive disorder: The budgetary impact on managed care. *Drug Benefit Trends* 2000;12:6BH-17BH. Reprinted with permission.

Figure 3. Meta-Analysis Showing Efficacy Rates of Extended-Release Venlafaxine (Ven XR), Selective Serotonin Reuptake Inhibitors (SSRIs), and Tricyclic Antidepressants (TCAs)

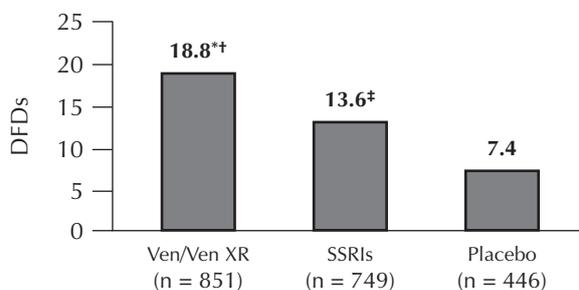


Outpatients and inpatients as assessed by 50% or more reduction in total Hamilton Rating Scale for Depression or Montgomery-Åsberg Depression Rating Scale.

* $P < .001$ versus SSRIs and $P < .001$ versus TCAs.

Source: Casciano R, Arikian SR, Tarride J-E, Casciano J, Doyle JJ. Antidepressant selection for major depressive disorder: The budgetary impact on managed care. *Drug Benefit Trends* 2000;12:6BH-17BH. Reprinted with permission.

Figure 4. Median DFDs by Treatment Group Over 8 Weeks



DFDs = depression-free days; SSRIs = selective serotonin reuptake inhibitors; Ven/Ven XR = venlafaxine and extended-release venlafaxine.

* $P < .0015$, Ven/Ven XR versus SSRIs.

+ $P < .0001$, Ven/VenXR versus placebo.

* $P = .0007$, SSRIs versus placebo.

$P < .0001$, overall difference across the 3 groups.

Source: Reference 13.

\$5647 per episode using primarily SSRIs and TCAs. They projected that an HMO would save between \$0.05 and \$0.16 per member per month at 15% venlafaxine XR utilization.⁸

In addition to a pharmacoeconomic benefit, venlafaxine XR was found to have a significantly better efficacy rate than either SSRIs or TCAs, as assessed by a 50% or more reduction in the Hamilton Rating Scale for Depression (HAM-D) score or Montgomery-Asberg Depression Rating Scale.⁸ Treatment of outpatients with venlafaxine XR yielded an overall efficacy rate of 73.7%, compared with 61.4% for SSRIs and 59.3% for TCAs (Figure 3). The relative inpatient efficacy rates mirrored the outpatient rates; treatment of inpatients with venlafaxine XR yielded an overall efficacy rate of 62.3%, compared with 58.6% for SSRIs and 58.2% for TCAs. The investigators concluded that, "Considering its lower expected cost per treated patient combined with its improved treatment outcomes, venlafaxine XR was determined to be more cost effective and exhibited dominance in the treatment of MDD when compared with SSRIs and TCAs as a class."⁸

A second study assessed the relative cost effectiveness of immediate-release venlafaxine, SSRIs, and TCAs in the treatment of MDD in 10 countries (Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom, United States, and Venezuela).⁹ A decision analytic model assessing the acute phase of MDD treatment within a 6-month period was used. Six decision-tree models were customized with country-specific estimates from a clinical management analysis, meta-analytic rates from 2 published meta-analyses,^{10,11} and a resource valuation of treatment costs representing the inpatient and outpatient settings within each country. The meta-analytic rates were applied to the decision analytic model to calculate the expected cost and expected outcomes for each antidepressant comparator. Cost effectiveness was determined using the expected values for both a successful outcome and a composite measure of outcome termed *symptom-free days*.

The authors found that initiating outpatient treatment of MDD with immediate-release venlafaxine yielded a lower expected cost compared with SSRIs and TCAs in all countries except Poland. The weighted average expected cost per patient for MDD treatment ranged from \$632 (Poland) to \$5647 (United States) during the 6-month acute phase.⁹ The estimated total budgetary impact for each 1% of venlafaxine utilization, assuming a population of 1 million MDD patients, ranged from \$1600 (Italy) to \$29,049 (United States).⁹ Within both the inpatient and outpatient treatment settings, immediate-release venlafaxine was a more cost-effective treatment of MDD than either SSRIs or TCAs. In addition, the results of this study indicated that increased utilization of venlafaxine in most settings across Europe and the Americas would have a favorable impact on healthcare payer budgets. This study confirmed the results of previous pharmacoeconomic analyses in its conclusion that the use of venlafaxine is a cost-effective strategy for the treatment of MDD in both inpatients and outpatients across various healthcare payer systems. Furthermore, initiating treatment with venlafaxine provides a lower-than-expected cost when total health system costs are considered in the analysis of alternate antidepressant agents. The superior pharmacoeconomic profile of venlafaxine may be attributed to its high success rate and low number of dropouts as a result of adverse effects.

In a similar study, within outpatient and inpatient treatment settings, venlafaxine XR was a more cost-effective treatment for MDD compared with the SSRIs and TCAs in 9 countries (Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, United Kingdom, United States, and Venezuela).¹² The estimated cost savings for each 1% increase in venlafaxine XR utilization, assuming a population of 1 million MDD patients, ranged from \$2820 (Italy) to \$37,313 (United States). The results indicate that increased use of venlafaxine XR in settings across the Americas and

Europe may have economic benefit to healthcare payers.

It may also be useful to evaluate the efficacy of venlafaxine compared with SSRIs and placebo in terms of the number of depression-free days (DFDs) during treatment. In a recent study, Mallick et al¹³ estimated DFDs using weekly scores on the 17-item HAM-D scale (see sidebar for more information). The study investigators assigned a value of 1 DFD to each day that a patient had a score of ≤ 7 (remission threshold), 0 DFDs to each day that a patient had a score of ≥ 15 (acutely symptomatic), and fractional DFDs proportionately to days that a patient had scores of 7 to 14. Weekly DFDs were aggregated over the 8-week study period to obtain cumulative (total) DFDs.

Study data were obtained from a meta-analysis of 8 pooled clinical studies; 4 of the studies were placebo controlled. The data showed that treatment with venlafaxine or an SSRI is associated with an increase in the number of DFDs compared with placebo (**Figure 4**). Furthermore, there was a significantly greater number of median DFDs during venlafaxine treat-

Association of DFDs with Remission

DFDs are expected to be positively associated with remission, in particular duration of maintained remission, measured in terms of HAM-D17 ≤ 7 criteria. To explore this hypothesis, Mallick et al¹³ examined DFDs in terms of remission defined as a score of 1 or 2 (low clinical global illness) on the Clinical Global Impression—Severity of Illness scale (CGI-S). Cumulative DFDs were compared across 4 groups of patients: those who attained and maintained CGI-S = 1 or 2 for ≥ 6 weeks through the end of the 8-week treatment; 4 to 5 weeks through the end of the 8-week treatment period; a transient period of time (< 4 weeks); or those who never attained CGI-S = 1 or 2. Patients who maintained CGI-S = 1 or 2 for longer time periods had more DFDs than did those with shorter, transient, or never-attained CGI = 1 or 2.¹³

ment than during SSRI or placebo treatment (18.8 versus 13.6 versus 7.4, respectively; $P = .0001$).¹³

Comparison of Healthcare Expenditures in Depressed Patients With and Without Anxiety

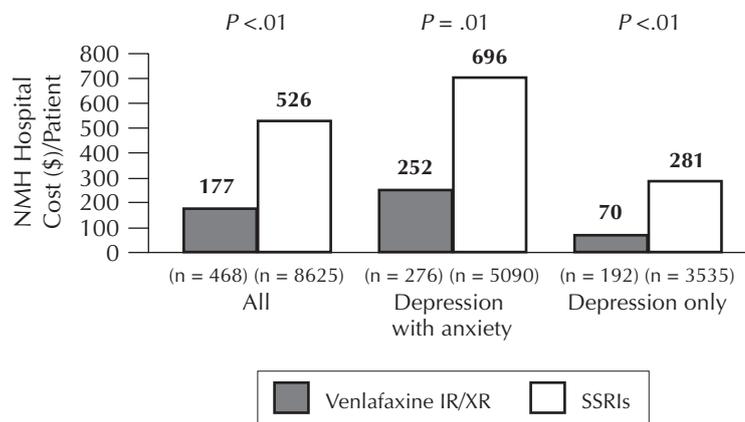
A comparison of expenditures in depressed patients with and without anxiety was conducted by analysis of the MEDSTAT MarketScan database.^{14,15} Of patients enrolled in a participating health or indemnity plan from 1994 to 1999, 90,933 patients were identified (using *International Classification of Diseases, Ninth Revision* diagnostic codes and prescription claims) who had a new depressive episode with or without anxiety (within 6 months). Data were based on US administrative claims of 2.3 million covered lives. Expenditures were estimated by the average amount paid per patient overall and separately for inpatient, outpatient, and pharmacy services during 6 months of antidepressant treatment. Multivariate models were used to examine statistical significance of the covariates (age, sex, region, presence of anxiety, number of psychiatric and medical comorbidities, and prior psychiatric-related hospitalizations) with respect to costs.

A pharmacoeconomic benefit for venlafaxine (immediate- or extended-release formulations) was observed regardless of the presence of comorbid anxiety.

Venlafaxine had lower inpatient nonmental health costs (\$177 versus \$526, $P < .01$, **Figure 5**) and comparable antidepressant medication costs (\$352 versus \$360, $P = .50$, **Figure 6**) relative to SSRIs.¹⁵ Among depressed patients with anxiety, venlafaxine had lower inpatient nonmental health costs (\$252 versus \$696, $P = .01$) and comparable antidepressant medication costs (\$351 versus \$371, $P = .22$) relative to SSRIs. Among depressed patients without anxiety, venlafaxine had lower inpatient nonmental health costs (\$70 versus \$281, $P < .01$) and comparable antidepressant medication costs (\$353 versus \$344, $P = .63$) relative to SSRIs. After controlling for other covariates, medical-related inpatient costs (log-transformed) for patients taking venlafaxine also appeared lower than those for patients taking SSRIs. No statistically significant differences in medication costs, gaps in treatment, or compliance rates (venlafaxine XR versus SSRIs) were noted.¹⁵

Based on the MEDSTAT MarketScan data, prior to therapy, patients given ven-

Figure 5. Venlafaxine Versus Selective Serotonin Reuptake Inhibitors (SSRIs): Differences in Nonmental Health (NMH) Costs



MEDSTAT MarketScan data.
Source: Reference 15.

lafaxine had more medical illnesses and psychiatric-related hospitalizations than those given SSRIs.^{14,15} Although total costs for patients on venlafaxine were expected to be higher, no statistically significant differences were observed. Expected cost savings attributed to venlafaxine use appeared to be in the medical-related hospitalizations. Possible reasons why a difference was observed in nonmental health inpatient costs include better overall medication compliance among patients on venlafaxine and a lower risk of hospitalization among patients taking venlafaxine relative to patients taking other antidepressant agents. These results were consistent with other observational studies that found a trend toward lower nonmental health-related expenditures with favorable compliance rates.¹⁶⁻¹⁸ Although these data are compelling, further study is needed to determine definitively whether venlafaxine use is associated with more favorable economic benefits over time relative to SSRI use.

Resource Use and Costs of Venlafaxine Versus TCAs After Switching From an SSRI

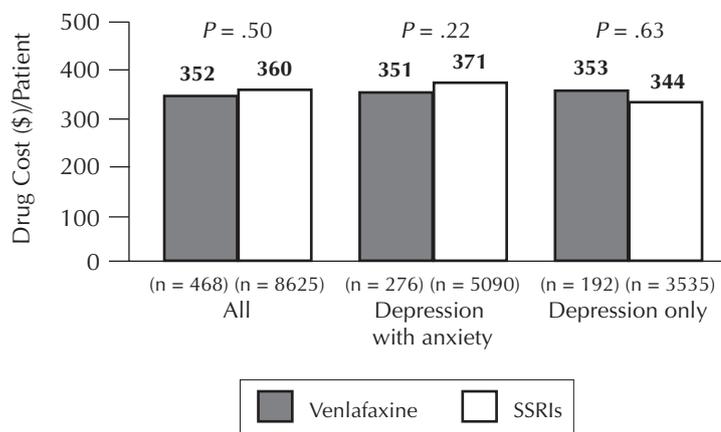
An analysis of computerized administrative claims data from 9 US healthcare plans was performed to compare the resource utilization and costs of venlafaxine therapy with that of TCA therapy in patients switched from an SSRI.¹⁹ The study sample consisted of patients who were diagnosed with depression and had received treatment with an SSRI for at least 2 months, followed by treatment with either venlafaxine or a TCA for at least 2 months. The analysis was based on 188 venlafaxine-treated patients and 172 TCA-treated patients. Mean depression-coded costs were significantly greater ($P = .0001$) for venlafaxine than for TCAs (\$1948 versus \$1396). In contrast, mean costs not coded for depression were significantly lower ($P = .0009$) for venlafaxine than for TCAs (\$4595 versus \$6677). These differences may, in part, be a result of differences in the way physicians code for depression. Undercoding of depression services by primary care physicians would tend to inflate

differences in depression-coded costs of venlafaxine therapy relative to TCA therapy by underestimating cost offsets because of better control of depressive symptoms or improved tolerability. Overall costs were not significantly different between venlafaxine and TCAs. The authors concluded that payer costs are similar among patients receiving venlafaxine and TCA therapy after SSRI therapy. The higher costs of venlafaxine therapy relative to TCA therapy may be offset by lower costs of other medical services.

Conclusion

Pharmacoeconomic data are mounting to show that the use of venlafaxine as a first-line therapy in the treatment of MDD may lower overall costs. Some studies demonstrate that venlafaxine is more effective in controlling depression than either SSRIs or TCAs, and that venlafaxine therapy is associated with fewer dropouts because of adverse events than SSRI or TCA therapy. In particular, the MEDSTAT MarketScan data demonstrated that potential cost savings associated with venlafaxine use appear to be related to fewer nonmental health hospitalizations in patients with major depression with or without anxiety.

Figure 6. Venlafaxine Versus Selective Serotonin Reuptake Inhibitors (SSRIs): Comparable Medication Costs



MEDSTAT MarketScan data.
Source: Reference 15.

These findings have enormous potential ramifications for the practicing physician. The evidence suggests that venlafaxine is an effective first-line therapy for major depression, from both clinical and pharmacoeconomic perspectives, in patients with or without comorbid anxiety. Compared with SSRIs, venlafaxine provides superior remission rates, lower risk of relapse, fewer dropouts as a result of adverse events or lack of efficacy, and dose flexibility allowing for titration to achieve an optimal response.

... REFERENCES ...

1. Murray CJL, Lopez AD. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press; 1996.
2. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. *J Clin Psychiatry* 1993;54:405-418.
3. World Health Organization. Fact sheet no. 130. Available at: <http://www.who.ch/programmes/inf/facts130.html>. Accessed January 7, 1999.
4. Rice DP, Miller LS. The economic burden of affective disorders. *Br J Psychiatry* 1995;27:34-42.
5. Wells KB, Hays RD, Burnam MA, et al. Detection of depressive disorder for patients receiving prepaid or fee for service care: Results from the Medical Outcomes Study. *JAMA* 1989;262:3298-3302.
6. Simon GE, Von Korff M, Wagner EH, et al. Patterns of antidepressant use in community practice. *Gen Hosp Psychiatry* 1993;15:399-408.
7. World Health Organization. Online database. Available at: <http://www.who.ch/programmes/mnh/mnh/ems/rates/unipolar.html>. Accessed June 7, 2001.
8. Casciano R, Arikian SR, Tarride J-E, Casciano J, Doyle JJ. Antidepressant selection for major depressive disorder: The budgetary impact on managed care. *Drug Benefit Trends* 2000;12:6BH-17BH.
9. Doyle JJ, Casciano J, Arikian S, Tarride J-E, Gonzalez MA, Casciano R. A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): A comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. *Value in Health* 2001;4:16-31.
10. Busse R, Howorth C, Schwartz FW. The future development of the rights-based approach to health care in Germany: More rights or fewer? In: Lenaghan J, ed. *Hard Choices in Health Care*. London, England: BMJ Publishing Group; 1997.
11. Ulrich V, Wille E. Healthcare reform and expenditures on drugs. The German situation. *PharmacoEconomics* 1996;10(suppl):81-88.
12. Casciano J, Doyle J, Arikian S, Casciano R. The health economic impact of antidepressant utilization from a payer's perspective: A multinational study. *Int J Clin Pract* 2001;5:292-299.
13. Mallick R, Entsuh R, Chen J. Depression-free days and CGI-S: A venlafaxine, SSRI, and placebo comparison. Proceedings of the 154th Annual Meeting of the American Psychiatric Association; May 5-10, 2001; New Orleans, LA.
14. Crown WH, Wan GJ, Berndt E, Finkelstein S, Ling D. Direct medical expenditures associated with the treatment of depressed patients with or without anxiety. Poster presented at: Annual Meeting of the American Society of Health-System Pharmacists; June 3-6, 2001; Los Angeles, CA.
15. Wan GJ, Crown WH, Berndt ER, Finkelstein SN, Ling D. Are venlafaxine and venlafaxine XR associated with lower hospitalization costs in depressed patients with or without anxiety compared to SSRIs? Poster presented at: World Assembly for Mental Health, the 26th Biennial Congress of the World Federation for Mental Health; July 22-27, 2001; Vancouver, BC, Canada.
16. Baker AM, Russell JM, Campbell, JK. Variance in treatment compliance and costs by antidepressant class: Analysis in an HMO setting. *Formulary* 2001;36:204-210.
17. Thompson D, Hylan TR, McMullen W, et al. Predictors of a medical offset effect among patients receiving antidepressant therapy. *Am J Psychiatry* 1998;155:824-827.
18. Crown WH, Berndt E, Finkelstein S, Ling D, Wan GJ. Differences in healthcare expenditures among patients treated for depression with or without anxiety [abstract]. *J Gen Intern Med* 2001;16(suppl 1):125.
19. Griffiths RI. Medical resource use and cost of venlafaxine or tricyclic antidepressant therapy. *Pharmacoeconomics* 1999;15:495-505.