Cost Savings With Nefazodone in Treating Depression

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Pharmacoeconomic analysis of antidepressant therapy is an important tool for ensuring the most cost-cognizant approach to treat a particular mental disorder. As the number of effective antidepressant compounds continues to grow, the drug selection process must consider not only the cost of the drug itself, but also costs associated with treatment failure and management of untoward and unexpected side effects. In economic studies conducted in North America and England using a decision analysis model and a direct annual cost model, nefazodone has been shown to have an impact on costs associated with depression when compared with imipramine and fluoxetine. Nefazodone also can reduce depression-related anxiety and agitation symptoms early in treatment, and, because it improves subjective and objective sleep measures, use of concomitant anxiolytics or sedative-hypnotics with nefazodone has been shown to be less frequent and less costly than with selective serotonin reuptake inhibitors.
(J Clin Psychiatry 2002;63[suppl 1]:48–51)

Analysis of the economic aspects of psychopharmacologic agents has become increasingly important in the overall approach of treating a particular mental disorder.[1,2] Today, practitioners have a number of effective antidepressant agents at their disposal to treat patients suffering from depression and associated anxiety disorders. The selective serotonin reuptake inhibitors (SSRIs) have overtaken the tricyclic antidepressants (TCAs) as the most commonly used antidepressants in clinical practice.[3] In addition to SSRIs, other new antidepressants, such as nefazodone, bupropion, venlafaxine, and mirtazapine, are effective for treating patients with depression. In this article, several economic analyses that have evaluated the cost impact of nefazodone versus imipramine and SSRIs for treating depression are reviewed. The potential cost savings with nefazodone as a treatment for depression, especially in patients with significant anxiety and sleep disturbance, also are analyzed.

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Supported by an unrestricted educational grant from Bristol-Myers Squibb Company.

Financial disclosure: Dr. Hales has served as a consultant for Bristol-Myers Squibb and has received honoraria from and served on the speakers/advisory boards for Bristol-Myers Squibb, SmithKline Beecham, Forest Pharmaceuticals, Pfizer, and Glaxo Wellcome. Dr. Hilty has served on the speakers/advisory boards for Wyeth-Ayerst, Pfizer, SmithKline Beecham, Bristol-Myers Squibb, and Glaxo Wellcome. Dr. Brunson is an employee of Bristol-Myers Squibb Company.

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COST-SAVINGS ANALYSES

At the time nefazodone was to be introduced in Canada in the mid-1990s, Anton and Revicki[4] used a decision model approach to evaluate its cost savings. These authors estimated cost and outcomes under a variety of clinical scenarios. Health care costs were represented by estimates of direct medical costs, whereas health outcomes were defined in terms of quality-adjusted life-years (QALYs). The authors defined the QALY as a measure of "expected survival, adjusted for the impact of different clinical events on patient function and well being."[4(p250)] This parameter measures both the change in quantity of life as reflected in decreased mortality and the change in quality of life as reflected in reduced morbidity. Quality adjustments were based on "utilities," a measure of the preference of an individual for a health state resulting from a particular treatment.[5,6]

Because nefazodone was newly approved in Canada, the authors wanted to determine its relative cost savings as compared with 2 currently available antidepressants, the SSRI fluoxetine and the TCA imipramine. The authors therefore went through the following steps: they identified the decision, established a time frame for their decision, structured the decision and its consequences over time, assessed the probability of the occurrence of each consequence in the model, determined the cost associated with each treatment and the value of each possible outcome, and compared the cost savings of the medications.

The results of this study showed that the average lifetime cost associated with imipramine was $52,111; with fluoxetine, $50,678; and with nefazodone, $50,664. Consequently, nefazodone was substantially less expensive than imipramine and slightly less expensive than fluoxetine. Using the

Table 1. Summary of Objective Electroencephalographic Sleep Measures With Nefazodone and Fluoxetine in Depressed Patients[a]

Variable	Nefazodone	Fluoxetine	p Value[b]
Number of awakenings	↓	↑	≤ .01
% Awake time[c]	↓	↑	≤ .01
% Stage I sleep	↓	↑	≤ .01
Sleep efficiency	↑	↓	≤ .01
Sleep latency	↔	↔	NS

[a]Data from references 12–14. Abbreviation: NS = not significant.
Symbols: ↓ = decrease, ↑ = increase, ↔ = no change.
[b]Difference between drugs in change from baseline.
[c]Includes awake and movement time by electroencephalogram.

various assumptions and parameters of their model, lifetime treatment with nefazodone yielded 13.90 QALYs compared with 13.79 QALYs for fluoxetine and 13.18 QALYs for imipramine. Finally, in evaluating the relative cost savings of the medications, when lifetime direct medical costs and the health consequences of treatment for the 3 antidepressants were considered, nefazodone was rated better than imipramine and fluoxetine. Revicki and colleagues[7] published comparable findings.

Montgomery and associates[8] conducted a similar study in England to compare the relative cost of nefazodone versus imipramine in treating depression. They used a model developed by Jonsson and Bebbington[9] to calculate the direct annual cost of treating depression. Costs were updated to 1994 standards, and the cost of nefazodone was substituted for that of paroxetine, which was included in the original study. The authors also substituted probabilities of adverse events and relapse reported in long-term, placebo-controlled studies of nefazodone from a Bristol-Myers Squibb data set.[10] Using updated costs and probabilities from continuation trials, the expected annual cost per successfully treated patient was £242 for nefazodone and £323 for imipramine. The expected annual cost of treatment with nefazodone was £218 and £254 with imipramine. Similar to the findings of Anton and Revicki,[4,7] Montgomery and colleagues[8] demonstrated that the annual cost of nefazodone treatment was lower than the annual cost for imipramine for patients who completed 6 to 8 weeks of antidepressant treatment and who were followed for at least 1 year.

In a more recent study, Revicki and colleagues[11] used the clinical decision analysis model previously discussed to evaluate the relative impact of nefazodone, fluoxetine, and imipramine in treating depression, using assumptions for managed-care settings. As in the earlier study,[4] nefazodone was a cost-saving treatment as compared with imipramine or fluoxetine. Fluoxetine was a more cost-saving intervention than imipramine, but was associated with slightly higher medical costs and less cost savings when compared with nefazodone.

These 3 studies are important for several reasons. First, they include estimates of health care costs and outcomes that are often not considered by medical groups or pharmacists when selecting a preferred antidepressant for the formulary. For instance, on the basis of drug costs alone, imipramine will always be less expensive than newer, branded antidepressants, such as nefazodone or fluoxetine. However, when the cost benefits of the outcomes achieved and the cost increases associated with treatment failures are considered, imipramine becomes a more expensive therapeutic choice. Consequently, studies such as those reviewed herein are important to bring to the attention of health care and pharmacy decision makers, because antidepressants that are viewed as more expensive based solely on the cost of the medication may be more cost-saving over the long term when health outcomes are included in the cost comparison.

EFFECTS OF NEFAZODONE ON DEPRESSION-RELATED SLEEP DISTURBANCES AND ANXIETY SYMPTOMS

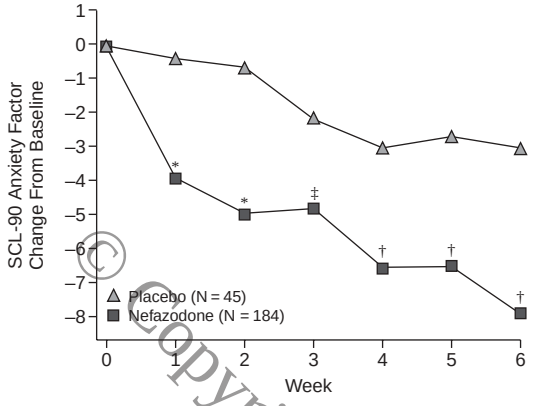
Nefazodone has been shown to have beneficial effects in treating depression-related sleep disturbances. Results of several studies have documented that nefazodone decreases the number of awakenings and the percentage of awake time and stage I sleep and increases sleep efficiency as compared with fluoxetine (Table 1).[12–14] Similar beneficial effects have been reported in healthy adults and in patients with major depressive disorder.[15]

Fontaine and colleagues[16] reported an early and sustained improvement of depression-related anxiety symptoms with nefazodone as compared with placebo after the first week of treatment; this improvement continued throughout the 6-week study (Figure 1). Fawcett and colleagues[17] also observed significant reductions in agitation with nefazodone early in the course of treatment, and these reductions remained statistically significant throughout treatment when compared with imipramine and placebo (Figure 2).

Use of Concomitant Medications

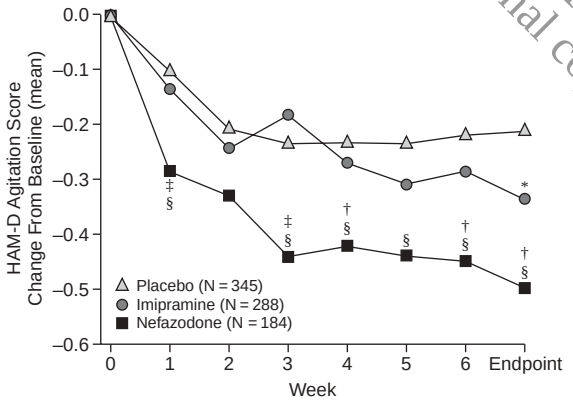
Clinically, as many psychiatrists have observed, as depression-related anxiety symptoms increase, the frequency and severity of depression-related sleep disturbance also increase. As the frequency and severity of sleep disturbances increase, the frequency of physicians' prescribing anxiolytics or sedative-hypnotics also increases. One group of investigators sought to retrospectively determine the prevalence of concomitant medication use in 80 elderly depressed patients who were diagnosed with depression and either agitation or anxiety.[18] Patients were receiving an SSRI (fluoxetine, paroxetine, or sertraline) or nefazodone. Ninety-eight percent of the 50 patients who were receiving an SSRI received concomitant medication, compared with only 26.7% of the 30 patients receiving nefazodone. Eight percent of the

Figure 1. Change From Baseline in Symptom Checklist-90 (SCL-90) Anxiety Factor Score in Patients With Depression (last observation carried forward)[a]



[a]Adapted with permission from Fontaine et al.[16] Baseline scores were 14.8 in the placebo group and 16.2 in the nefazodone group. The nefazodone dose ranged from 100 to 500 mg/day (mean = 460 mg/day).
*p < .01 vs. placebo.
†.01 < p < .05 vs. placebo.
‡.05 < p < .10 vs. placebo.

Figure 2. Mean Change From Baseline in Hamilton Rating Scale for Depression (HAM-D) Agitation Score (item 9) in Patients With Depression[a]

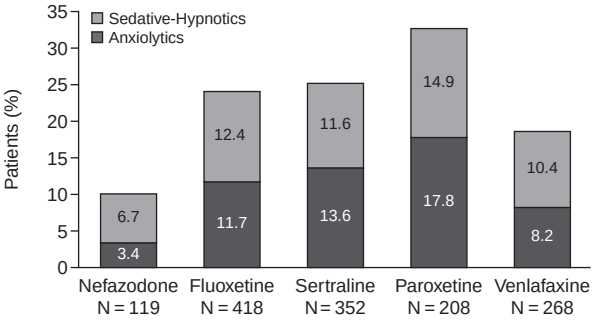


[a]Reprinted with permission from Fawcett et al.[17]
*p ≤ .05 vs. placebo. §p ≤ .01 vs. placebo. †p ≤ .05 vs. imipramine. ‡p ≤ .01 vs. imipramine.

SSRI-treated patients reported continued anxiety and 6% reported sleep disturbances. None of the nefazodone-treated patients reported either anxiety symptoms or sleep difficulties.

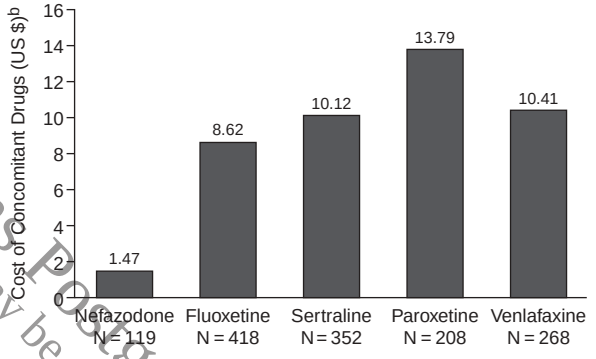
A larger systematic review[19] involved a random sample of California Medicaid (MediCal) patients from January 1, 1995, through May 31, 1995, to determine both the percentage of patients on treatment with various antidepressant agents receiving an antianxiety or sedative-hypnotic agent and the cost associated with concomitant use within the first 30 days of antidepressant treatment. Nefazodone-treated patients had the smallest percentage of patients taking either a sedative-hypnotic or an anxiolytic (Figure 3). Higher rates were noted in patients taking SSRIs and venlafaxine. When the cost of concomitant medications was calculated, nefazodone was a less expensive treatment alternative (Figure 4).

Figure 3. Concomitant Use of Anxiolytic or Sedative-Hypnotic Drugs by Patients on Antidepressant Therapy (5% random sample of the California Medicaid program, 1/1/95 to 5/31/95)[a]



[a]Adapted with permission from Lian et al.[19]

Figure 4. Total Cost (US $) of Concomitant Anxiolytic and Sedative-Hypnotic Drugs in Patients on Antidepressant Therapy (5% random sample of the California Medicaid program, 1/1/95 to 5/31/95)[a]



[a]Data from Lian et al.[19]
[b]Cost (in US $) within 30 days per patient.

NEFAZODONE IN CHRONIC DEPRESSION

The relative cost savings of nefazodone, the cognitive behavioral-analysis system of psychotherapy (CBASP), and their combination in chronically depressed individuals has also been evaluated. In one study,[20] the direct treatment cost per patient was $770 for nefazodone, $1800 for CBASP, and $3400 for their combination. Thus, direct treatment costs were lowest for nefazodone monotherapy, and treatments utilizing nefazodone, alone or in combination with CBASP, were the most cost saving.

SUMMARY

In studies conducted in Canada, England, and the United States, nefazodone has been shown to be a cost-saving treatment for depression when compared with imipramine and fluoxetine on the basis of a decision analysis model and a direct annual cost model. In addition, nefazodone reduces depression-related anxiety and agitation symptoms early in treatment, even before therapeutic doses are achieved. Because it also improves subjective and objective sleep measures, the use of concomitant anxiolytics or sedative-hypnotics with nefazodone has been shown to be less frequent and less costly than with SSRIs.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Sclar DA, Skaer TL, Robison LM, et al. Economic appraisal of antidepressant pharmacotherapy: critical review of the literature and future directions. Depress Anxiety 1998;8(suppl 1):121–127
2. Jones MT, Cockrum PC. A critical review of published economic modeling studies in depression. Pharmacoeconomics 2000;17:555–583
3. Lawrenson RA, Tyrer F, Newson RB, et al. The treatment of depression in UK general practice: selective serotonin reuptake inhibitors and tricyclic antidepressants compared. J Affect Disord 2000;59:149–157
4. Anton SF, Revicki DA. The use of decision analysis in the pharmacoeconomic evaluation of an antidepressant: a cost-effectiveness study of nefazodone. Psychopharmacol Bull 1995;31:249–258
5. Feeny D, Torrance GW. Incorporating utility-based quality of life assessments in clinical trials: 2 examples. Med Care 1989;27(suppl 3):190–204
6. Froberg D, Kane R. Methodology for measuring health-state preferences, 3: population and context effects. J Clin Epidemiol 1989;42:585–592
7. Revicki DA, Brown RE, Palmer W, et al. Modelling the cost effectiveness of antidepressant treatment in primary care. Pharmacoeconomics 1995;8: 524–540
8. Montgomery SA, Brown RE, Clark M. Economic analysis of treating depression with nefazodone v imipramine. Br J Psychiatry 1996;168:768–771
9. Jonsson B, Bebbington PE. What price depression? the cost of depression and the cost effectiveness of pharmacological treatment. Br J Psychiatry 1994;164:665–673
10. Anton SF, Robinson DS, Roberts DL, et al. Long-term treatment of depression with nefazodone. Psychopharmacol Bull 1994;30:165–169
11. Revicki DA, Brown RE, Keller MB, et al. Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings. J Clin Psychiatry 1997;58:47–58
12. Armitage R, Yonkers K, Cole D, et al. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17: 161–168
13. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. J Clin Psychiatry 1997;58:185–192. Correction 1997;58:275
14. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry 1998;44:3–14
15. Armitage R. The effects of nefazodone on sleep in depressed patients and healthy controls. Int J Psychiatry Clin Pract 1999;3:73–79
16. Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994;55:234–241
17. Fawcett J, Marcus RN, Anton SF, et al. Response of anxiety and agitation symptoms during nefazodone treatment of major depression. J Clin Psychiatry 1995;56(suppl 6):37–42
18. Frenchman IB, Prince T. Retrospective chart review comparing nefazodone to 3 selective serotonin reuptake inhibitors for treatment of depression with agitation or anxiety. Consult Pharm 1998;13:701–704
19. Lian JF, Hales RE, McQuade RD, et al. Nefazodone therapy and concomitant anxiolytic and sedative/hypnotic drug therapy in patients with depression. Primary Psychiatry 1999;6:75–87
20. Russell JM, Crown WH, Borian FE, et al. Economic aspects of nefazodone, Cognitive Behavioral Analysis System of Psychotherapy and their combination for the treatment of chronic major depression. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 17, 2000; Chicago, Ill. Abstract NR501:193–194