Cost-Effectiveness of Newer Antidepressants Compared With Tricyclic Antidepressants in Managed Care Settings

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Background: Our aim was to determine the cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care organization settings.

Method: We employed cost-utility analysis based on a clinical decision analysis model derived from published medical literature and physician judgment. The model, which represents ideal primary care practice, compares treatment with nefazodone to treatment with either imipramine or fluoxetine or to a step approach involving initial treatment with imipramine followed by nefazodone for treatment failures. The outcome measures were lifetime medical costs, quality-adjusted life years (QALYs), and costs per QALY gained.

Results: The base case analysis found that nefazodone treatment had $16,669 in medical costs, compared with $15,348 for imipramine, $16,061 for the imipramine step approach, and $16,998 for fluoxetine. QALYs were greatest for nefazodone (14.64), compared with 14.32 for imipramine, 14.40 for the step approach, and 14.58 for fluoxetine. The cost-effectiveness ratio comparing nefazodone with imipramine was $4065 per QALY gained. The cost-effectiveness ratio comparing nefazodone with the step approach was $2555 per QALY gained. There were only minor differences in costs and outcomes between nefazodone and fluoxetine, with nefazodone resulting in $329 fewer costs and 0.06 more QALYs. The cost-effectiveness ratios comparing fluoxetine with imipramine and with the step approach were $6346 per QALY gained and $5206 per QALY gained, respectively. In the sensitivity analyses, the cost-effectiveness ratios comparing nefazodone and imipramine ranged from $2572 to $5841 per QALY gained. The model was most sensitive to assumptions about treatment compliance rates.

Conclusion: The findings suggest that nefazodone is a cost-effective treatment compared with imipramine or fluoxetine treatment for major depression. Fluoxetine is cost-effective compared with imipramine treatment, but is estimated to have slightly more medical costs and less effectiveness compared with nefazodone. The basic findings and conclusions do not change even after modifying key model parameters.

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Depressive disorders are one of the most frequent reasons for visits in primary care settings[1] and are associated with high rates of health services utilization,[2,3] increased disability, and decreased functioning and well-being.[4–6] In 1990, the direct medical cost of treating depression in the United States was estimated at $12.4 billion.[7] Antidepressant medications are effective in treating depression, but many patients are not diagnosed[2,8–10] or are inadequately treated.[11–13]

Tricyclic antidepressants (TCAs) are frequently used in treating depression and are effective in 60% to 80% of patients.[14–16] The TCAs have troublesome side effects, and some patients cannot tolerate extended treatment. The introduction of serotonin selective reuptake inhibitors (SSRIs) and other new medications such as venlafaxine and nefazodone has increased available depression treatment options. Compared with TCAs, the SSRIs[17–21] and nefazodone[22–26] have comparable clinical efficacy and fewer side effects.[18,19,27] The SSRIs and newer antidepressants have significantly higher pharmacy acquisition prices than the TCAs. Selection of antidepressant treatment depends on physician judgment of patient response and tolerance and, increasingly, considerations of medical costs in managed care organizations (MCOs).

The higher prices of the newer antidepressants have led to questions about their value. Given the concern about limitations in health care resources, the cost-effectiveness of new antidepressants must be demonstrated before they are widely used in primary care and managed care practice.[28,29] Some countries, such as Canada and Australia, incorporate results from cost-effectiveness studies into decisions about registration, reimbursement,

and pricing. MCOs also need information from cost-effectiveness studies to assist formulary decision making.

There is little research on the cost-effectiveness of different antidepressant medications. The research conducted largely depends on clinical decision modeling of medical costs and outcomes.[30–35] Although it is recognized that prospective, randomized studies involving measurement of depression and health status outcomes and medical service utilization and costs are the best approach to evaluating cost-effectiveness,[36,37] no prospective studies have been published. Kamlet et al.[30] and Hatziandreu et al.[31] examined the cost-effectiveness of maintenance therapy compared with episodic antidepressant treatment in patients with recurrent major depression. Jonsson and Bebbington[32] evaluated paroxetine and imipramine treatment, but modeled only short-term success or failure rates and medical costs. Since depression is a chronic and lifetime psychiatric disorder, to be relevant, studies need to consider long-term effectiveness and medical costs. Revicki and colleagues[33,34] have examined the cost-effectiveness of nefazodone by using a lifetime decision model for treatment of depression in Canada. Treatment patterns and the health care system are sufficiently different between the United States and Canada to warrant the current study.

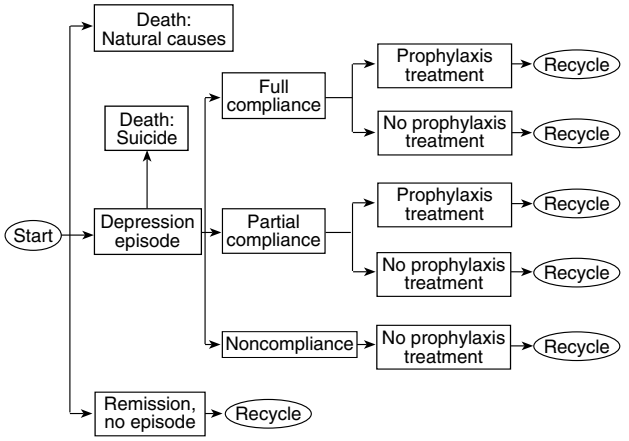
This study was designed to evaluate the cost-effectiveness of three antidepressants, nefazodone, fluoxetine, and imipramine, for the treatment of major depression in MCOs. Because many MCOs have guidelines restricting the use of SSRIs, we also estimated the medical costs and outcomes expected in a step approach where patients with depression are first treated with a TCA and are only prescribed an SSRI for lack of response or for side effect intolerance. A clinical decision model was constructed to estimate lifetime medical costs and quality-adjusted life years (QALYs) associated with the different antidepressants based on the medical literature and clinician judgment.

METHOD

A clinical decision analysis model was developed to simulate the clinical management pathways and pattern of recurrences of major depression to estimate the lifetime health outcomes and medical costs of different antidepressant treatments. Decision models are useful techniques for evaluating the cost-effectiveness of treatments for chronic diseases where only intermediate outcomes are available.[36,38–40]

The decision model compares antidepressant treatment among nefazodone, imipramine, or fluoxetine or a step approach where patients are initially prescribed imipramine and receive nefazodone if imipramine treatment fails. Nefazodone is a recently approved antidepressant that is a potent antagonist of 5-HT_2 postsynaptic receptors and an inhibitor of the reuptake of serotonin and norepinephrine and has comparable efficacy with other antidepressants.[22–26] Nefazodone compared with fluoxetine causes less initial anxiety and sexual dysfunction and has a lower prescription price. However, nefazodone must be given twice a day compared with once-a-day dosing for fluoxetine. Imipramine was selected because of its widespread use and low price and its frequent use as a comparator in randomized clinical trials of new antidepressants. Fluoxetine was selected because it is the SSRI most frequently used to treat depression in the United States.

Figure 1. Simplified Economic/Clinical Decision Model for Depression Treatment



The perspective for the pharmacoeconomic analysis is the U.S. MCO setting; therefore, only direct medical costs are considered in the model. Health outcomes are expressed as QALYs, and costs are expressed in 1994 U.S. dollars. The model estimates cumulative medical costs and QALYs for each treatment approach. All costs and QALYs are discounted to present value using a 5% rate.

Clinical Decision Model

A Markov state-transition model was constructed to track QALYs and medical costs as they accrue over time. The clinical decision model is based on earlier economic models[31,34] with modifications for the northeastern and northwestern U.S. MCO environment. Figure 1 depicts the sequence of events and health states that an individual can experience in the economic/clinical decision model. The length of each cycle is 1 year. Unless an episode of major depression occurs, individuals remain in remission and have some probability of death, according to life tables. Individuals experiencing a depression episode can commit suicide or enter acute and continuation antidepressant treatment. A key underlying model assumption is that an adequate antidepressant effect is dependent on patient compliance. The more compliant a patient is with all

aspects of the treatment, the more likely that she or he will receive maximum benefit from antidepressant therapy. Transition to maintenance therapy is dependent on treatment adherence and completion of continuation therapy.

The model reflects ideal clinical practice; that is, treatment for each episode continues for 9 months, regardless of treatment arm, based on recently suggested guidelines for the treatment of major depression in primary care.[16] Therefore, in the model, all patients receive 3 months of acute treatment and 6 months of continuation antidepressant therapy. Patients entering maintenance treatment continue their antidepressants for an additional 27 months.

The model estimates the lifetime medical costs and QALYs of 30-year-old women who have had one previous episode of major depression treated by primary care physicians in a staff model MCO. Women were selected because of the relatively high prevalence of diagnosed depression in this population[1] and to simplify the estimation of survival, which is based on standard life tables.

Data Sources

Data for the model came from the medical literature and physician panel members (M.B.K., J.G., L.C., R.E.H.). Data include information on medical resource use and costs, probabilities for the model, health utilities, and QALYs. To the extent possible, data for the model were taken from the published literature.

The physician panel consisted of two primary care physicians, four psychiatrists, and one clinical pharmacologist with experience in the diagnosis and treatment of major depression. Two of the panel members were from MCOs. A modified Delphi technique[41] was used to obtain estimates for the model. Panel members were provided a description of the decision model and summaries of the medical literature and were asked to complete a questionnaire on depression treatment. Questionnaire responses were summarized and returned to panel members for review before the panel meeting. During the meeting, each estimate was discussed until consensus was reached. Panel members provided estimates for model parameters not available in the literature (e.g., treatment compliance rates), critiqued the model structure, and supplied information on practice patterns and the use of medical services in the treatment of depression in MCOs.

Antidepressant Treatment Response

The literature suggests that 60% to 80% of patients treated with an antidepressant respond to treatment.[14–21,22–25] Sixty percent to 70% of patients who do not respond to the antidepressant first prescribed respond to a second or third antidepressant, resulting in an overall response rate of about 88%.[16] The remaining 12% are considered treatment resistant. This proportion of patients is the same regardless of treatment group.

Compliance With Antidepressant Treatment

A key part of the depression model is patient compliance with both medication regimen and physician visits. Patients treated for depression can either drop out of treatment altogether or be fully compliant, partially compliant, or minimally compliant with their antidepressant therapy. Treatment discontinuation and, for those patients not discontinuing, compliance with all aspects of the treatment regimen are treated separately in the model. Full compliance was defined as taking 80% or more of prescribed treatment, partial compliance was defined as taking 50% to 79% of treatment, and minimal compliance was defined as taking less than 50% of treatment. The probability of a particular compliance state depends upon the patient's drug therapy and its associated side effects. The physician panel estimated that for imipramine-treated patients, 30% would drop out of treatment within 6 weeks, and of the remainder, 40% would be fully compliant, 30% would be partially compliant, and 30% would be minimally compliant. These estimates are comparable with the discontinuation rates associated with TCAs reported in a meta-analysis[42] and recent prospective data.[43] Previous research in primary care settings suggests that between 20% and 60% of patients discontinue treatment within the first month.[11–13,44] Lin et al.[44] found that 28% of primary care patients discontinued their antidepressant within 30 days, and 44% were not taking their medication by 3 months. More than 60% reported that they stopped taking antidepressants because of side effects.[44] Recent evidence suggests that there may be greater compliance with SSRIs or nefazodone compared with TCAs.[12,17,20,26] Nefazodone is prescribed twice daily, and fluoxetine is prescribed once daily. Little difference in patient compliance has been observed between once-a-day and twice-a-day dosing regimens[44,45]; therefore, we assumed that compliance for fluoxetine and nefazodone is equal. The clinical panel believed that compliance would be somewhat higher for nefazodone and fluoxetine: 20% of the patients would discontinue treatment by 6 weeks, and of those remaining, 50% would be fully compliant, 30% would be partially compliant, and 20% would be minimally compliant. These discontinuation rates have been demonstrated in a recent prospective study.[43]

The model assumes that patients move from one compliance state to another over the course of future depression episodes. Table 1 summarizes the transitional probabilities by initial compliance state in the model for each treatment as estimated by the physician panel. These transitional probabilities are used to estimate all subsequent compliance states, regardless of treatment, after the initial depression episode in the model.

Major Depression Episodes in the Model

Initial depression episode. The probabilities of the first depression episode in the model were derived from 5-year epidemiologic data.[46,47] Lavori et al.[47] report that for per-

Table 1. Transitional Probabilities of Compliance With Antidepressant

Initial Compliance State	Transitional Compliance State (%)		
	Full	Partial	Minimal
Full compliance	80	10	10
Partial compliance	20	60	20
Minimal compliance	15	25	60
Treatment dropout[a]	10	20	20

[a]Assume that 50% of treatment dropouts will also discontinue treatment for future depression episodes.

sons with one previous episode of depression, 28% will have another episode within 1 year with cumulative rates of 43% after 2 years, 52% after 3 years, 59% after 4 years, and 62% after 5 years. Persons with two or more episodes have a 1-year rate of 39% and cumulative rates of 60% after 2 years, 68% after 3 years, 73% after 4 years, and 82% after 5 years.[47] Approximately 10% of patients may have just one depression episode over their lifetimes, and another 10% to 12% are resistant to psychopharmacologic treatment alone and require a combination of electroconvulsive treatment and pharmacotherapy.[14,16] The initial-episode part of the model was identical for each treatment arm. The model assumes that 12% of patients exposed to each antidepressant will be treatment resistant and will remain in this state for the rest of their lives.

Subsequent depression episodes. The probability of experiencing a new episode of major depression depends on the length of time since the previous episode and the number of previous episodes.[46–51] Patients with a history of recurrent depression have a higher risk for experiencing additional episodes.[16,46,51–53] The physician panel indicated that recurrence of depression, while depending on patient characteristics and the severity of depression, was based on whether the patient receives adequate therapy independent of antidepressant medication. In the model, we assume that adequacy of antidepressant therapy is mostly determined by patient compliance. There are inadequate data on the relationship between compliance with antidepressant treatment and recurrence of depression episodes, and existing epidemiologic studies do not address patient compliance. Based on physician judgment, the model assumes that patients who were fully compliant with all aspects of their antidepressant treatment have a 15% rate of recurrence over a 12-month period following remission/recovery and end of antidepressant therapy. Patients who were partially compliant have a rate of 25%, and those who were minimally compliant have a 35% rate of recurrence over a 12-month period. Patients who discontinue treatment by 4 to 6 weeks have a depression recurrence rate of 50% over the next 12 months.

Suicide Probability

It was assumed that persons will be at risk for suicide during an episode of major depression. About 15% of persons hospitalized for treatment of major depression commit suicide.[16,54,55] Although TCAs are potentially lethal, and the SSRIs and nefazodone are safer than TCAs when taken in overdose,[27,54,56] there is no evidence that suicide attempts or completions differ by antidepressant.[54] Therefore, we assumed suicide rates of 0.85% per depression episode regardless of treatment, with a cumulative lifetime rate of 15% for the subset of patients with major depression who had been hospitalized.[55]

Maintenance Treatment

The panel estimated that only 75% of fully compliant patients complete continuation therapy, and of these, 50% enter maintenance treatment, regardless of the drug regimen. For partially compliant patients, 50% complete continuation therapy, and only 30% of these patients receive maintenance therapy. For the minimally compliant patients, 25% complete continuation treatment, and of these patients, only 10% enter maintenance therapy. The available literature on long-term treatment was used to estimate dropout and recurrence rates. The rates of dropout from maintenance treatment were estimated at 12.9% for nefazodone, 25.9% for imipramine, and 14.6% for fluoxetine. These rates were obtained from the weighted discontinuation rates for adverse events or lack of efficacy from long-term studies of nefazodone,[26,27] fluoxetine,[16,17] or imipramine.[16,26,51–53] Rates were weighted by treatment group sample size before aggregation.

Depression recurrence rates for patients on maintenance treatment were estimated, using these same sources, as 25.8% for nefazodone, 32.0% for imipramine, and 26.1% for fluoxetine.[16,17,26,27,51–53] For untreated groups, we used data on recurrence of major depression for placebo groups (57.7%) in long-term clinical trials.[16,17,20,26,51–53] The probability of having an episode of depression if the patient was not compliant with maintenance treatment was the same for each drug (57.7%). Patients complying with maintenance therapy remain on treatment for 27 months.

Medical Resource Use and Costs

The physician panel estimated the resources that would be used for acute treatment of depression (3 months), continuation treatment (6 months), and maintenance treatment (27 months) for patients receiving either nefazodone, imipramine, or fluoxetine. These practice patterns comply with recent recommendations for the treatment of depression in primary care.[16] Appendix 1 lists by compliance category and occurrence of a depression episode the annual number and type of physician visits, proportion hospitalized and length of hospital stay, proportion receiving ECT and number of sessions, laboratory costs, and number of days receiving pharmacotherapy. In the model, patients were assumed to have access to short-term psychological counseling (7 sessions) as needed.

The resource costs were based on the data from two MCOs and national cost data from the Health Care Financing Administration. Appendix 2 includes the costs by resource unit. The total pharmacy cost of nefazodone was $1.56 per day, fluoxetine $1.84 per day, and imipramine $0.38 per day. All future costs were discounted to present value using a rate of 5%.

A treatment cost of $2098 was assumed for successful suicides related to depression[57] and $99 for deaths from causes other than suicide. Complete data on the annual costs by outcome in the model are summarized in Appendix 3. Death from other causes was assumed to occur at 6 months, resulting in one half the cost of remission. The annual costs of remission ($198) and treatment resistance ($7417) were identical regardless of treatment. The annual cost of nefazodone episodic treatment ranged from $1078 to $1628, depending on compliance state. Comparable costs for imipramine were $966 to $1470; for fluoxetine, $1130 to $1725; and for the imipramine step approach, $1196 to $1746. Patients who dropped out of treatment consumed $822 for nefazodone, $772 for imipramine, $837 for fluoxetine, or $940 for the step approach. Maintenance therapy costs were $739 to $1255 depending on the specific antidepressant.

Utilities and Calculation of Annual QALYs

Seventy patients with major depression provided standard gamble utilities for depression-related health states.[34] All patients completed at least 8 weeks of antidepressant therapy and were recruited from physician practices in Toronto, Ontario, and San Diego, California. Eleven possible health states were considered in the model (see Table 2). Each hypothetical state was framed in terms of a 1-month duration and described depression symptoms, functioning and well-being, and medical therapy, including any side effects of treatment. The most frequently reported side effects of each medication were included in the health states descriptions. For imipramine, dry mouth, dizziness and light-headedness, lethargy and daytime drowsiness, blurry vision, constipation, jitteriness, and rapid heartbeat were included. For fluoxetine, side effects included were nausea, nervousness and jitteriness, troubled sleep, headaches, loss of appetite, and lethargy and fatigue. For nefazodone, side effects included lethargy and fatigue, dizziness and light-headedness, dry mouth, and nausea. The health states were reviewed by physicians to ensure fair and accurate descriptions of depression-related symptoms and treatment side effects.

Patients first rated each health state on a 100-point rating scale. This was used as an exercise to familiarize the patients with the health states. Next, for each state, patients were given a choice between living in the hypothetical state for 1 month and a gamble between full health and untreated depression for 1 month. Probabilities of untreated depression and full health were then varied sequentially until the respondent was indifferent about the choices.[58–60] After assigning utilities for the temporary health states, the patients were asked to rate untreated depression using a gamble between full health and death. In this case, the duration of the health state was the individual's lifetime. Using the utility obtained for untreated depression, we recalibrated the utilities for the other health states to place them on the death/full-health scale.

Table 2. Standard Gamble Utilities for Depression-Related Hypothetical Health States Based on Responses From 70 Patients

Health State	Utility
Complete health	1.00[a]
Remission from depression symptoms, no treatment	0.89
Depression symptoms at 1 month	
Nefazodone treatment	0.73
Fluoxetine treatment	0.72
Imipramine treatment	0.67
Depression symptoms at 3 months	
Nefazodone treatment	0.82
Fluoxetine treatment	0.79
Imipramine treatment	0.73
No depression symptoms	
Nefazodone maintenance treatment	0.87
Fluoxetine maintenance treatment	0.86
Imipramine maintenance treatment	0.80
Depression symptoms, no treatment	0.31
Death	0.00[a]

[a]Reference health state.

The patients assigned a utility of 0.31 to untreated depression (Table 2). A year on prophylaxis therapy with nefazodone was rated at 0.87; comparable utilities for imipramine and fluoxetine were 0.80 and 0.86, respectively. The utility for a year in remission and under no treatment was 0.89. QALYs were assigned to each year in the model depending on the probability of events (e.g., recurrence of major depression) and treatment arm. Future QALYs were discounted to present value using a 5% rate. Annual QALYs used in the model are summarized in Appendix 3.

RESULTS

Base Case Analysis

Under the base case assumptions, the estimated lifetime costs (discounted at 5%) were lowest for imipramine treatment ($15,348) and the step approach ($16,061). Treatment with nefazodone was estimated at $16,669, and treatment with fluoxetine was estimated at $16,998. QALYs were greatest for treatment with nefazodone (14.64), compared with 14.32 QALYs for imipramine, 14.40 QALYs for the step approach, and 14.58 QALYs for fluoxetine.

Nefazodone-treated patients cost $1321 more over their lifetime than imipramine-treated patients and resulted in 0.32 more QALYs. The cost-effectiveness ratio

Table 3. Sensitivity Analyses Varying Model Duration*

Model Duration (y)	Imipramine (I)		Imipramine Step (IS)		Fluoxetine (F)		Nefazodone (N)		Cost-Utility Ratios[a]				
	Cost	QALYs	Cost	QALYs	Cost	QALYs	Cost	QALYs	N vs I	N vs IS	N vs F	F vs I	F vs IS
5	$3079	3.548	$3192	3.557	$3285	3.598	$3220	3.605	$2474	$583	NA	$4120	$2268
10	$6153	6.321	$6346	6.361	$6593	6.421	$6463	6.439	$2627	$1500	NA	$4400	$4167
15	$8581	8.462	$8871	8.532	$9293	8.605	$9107	8.634	$3058	$2314	NA	$4979	$5781
20	$10,466	10.112	$10,852	10.207	$11,423	10.288	$11,194	10.325	$3418	$2898	NA	$5438	$7049

*All costs and QALYs are discounted to present value using a 5% rate.
[a]Incremental cost-utility ratio from the perspective of nefazodone or fluoxetine. NA indicates cost savings to produce a QALY. Positive values indicate the additional cost of producing a QALY.

comparing nefazodone with imipramine was $4065 per QALY gained. Nefazodone also cost $608 more than the step approach, but yielded 0.24 additional QALYs in the lifetime model. The cost-effectiveness ratio comparing nefazodone with the step approach was $2555 per QALY gained. There were only minor differences in costs and QALYs between fluoxetine and nefazodone.

For the lifetime model, fluoxetine-treated patients cost $1650 more than imipramine-treated patients and resulted in 0.26 more QALYs. The cost-effectiveness ratio comparing fluoxetine with imipramine was $6346 per QALY gained. Fluoxetine was more expensive than the step approach and resulted in 0.18 more QALYs. The cost-effectiveness ratio comparing fluoxetine with the step approach was $5206 per QALY gained.

A series of analyses were performed, using base case estimates, in which the duration of the model was varied from 5 years to 20 years. Length of time used in the economic analysis changed the results but did not change the overall conclusion of the cost-effectiveness analysis (Table 3). The cost-effectiveness ratios ranged from $2474 per QALY gained to $3418 per QALY gained when nefazodone was compared with imipramine. When the step approach was compared with nefazodone therapy, cost-effectiveness ratios ranged from $583 to $2898 per QALY gained. Fluoxetine compared with imipramine resulted in cost-effectiveness ratios from $4120 to $5438 per QALY gained. Compared with the step approach, fluoxetine had cost-effectiveness ratios between $2268 to $7049 per QALY gained. The cost-effectiveness ratios were lower for shorter duration models. Regardless of model duration, nefazodone was always cost saving compared with fluoxetine, but the actual differences in costs (range, $85 to $229) and QALYs (range, 0.007 to 0.037) were small.

Sensitivity Analysis

Discount rate. The analyses were repeated using a 0% and 10% discount rate (not shown). Regardless of the discount rate, nefazodone remained cost saving and resulted in greater QALYs compared with fluoxetine. Cost-effectiveness ratios comparing nefazodone and imipramine ranged from $3519 per QALY gained (at a 0% discount rate) to $5226 per QALY gained (at a 10% discount rate). The cost-effectiveness ratios comparing nefazodone with the step approach were $927 per QALY gained and $2762 per QALY gained for 0% and 10% rates, respectively. Cost-effectiveness ratios comparing fluoxetine and imipramine were $6699 per QALY gained (0% discount rate) and $5545 per QALY gained (10% discount rate). The cost-effectiveness ratios comparing fluoxetine with the step approach were $14,192 per QALY gained (0% discount rate) and $2219 per QALY gained (10% discount rate).

Compliance rates. A key parameter of the clinical decision model is estimated treatment-compliance rates. These rates were varied systematically to determine their effect on the cost-effectiveness ratios. First, we assumed that patients treated by any of the three antidepressants were fully compliant (Table 4). Under this assumption, the cost per QALY gained for nefazodone was $3167 compared with imipramine. Comparing nefazodone and the imipramine step approach resulted in a cost-effectiveness ratio of $2762 per QALY gained. Nefazodone therapy resulted in $388 fewer medical costs and 0.07 more QALYs compared with fluoxetine. Assuming full compliance for all treatments, fluoxetine compared with imipramine had a cost-effectiveness ratio of $4595 per QALY gained. The cost per QALY gained for fluoxetine was $5554 compared with the step approach.

When compliance rates for nefazodone were made equal to the compliance rates for imipramine in the base case analysis, nefazodone treatment had a cost-effectiveness ratio of $5096 per QALY gained compared with imipramine. The cost-effectiveness ratio comparing nefazodone with the step approach became $3300 per QALY gained. Fluoxetine still cost $432 more than nefazodone, but resulted in 0.03 additional QALYs.

The cost-effectiveness ratio comparing imipramine with nefazodone equaled $4188 per QALY gained when the compliance rates for imipramine were increased to those of base case nefazodone. The cost-effectiveness ratio for the imipramine step approach compared with nefazodone was now $2544 per QALY gained. Under this assumption, the cost-effectiveness ratio comparing fluoxetine with imipramine was $6576 per QALY gained. The cost-effectiveness ratio for the step approach became $5206 per QALY gained.

Table 4. Summary of Sensitivity Analyses for U.S. Antidepressant Treatment Model*

Sensitivity Analyses	Imipramine (I)		Imipramine Step (IS)		Fluoxetine (F)		Nefazodone (N)		Cost-Utility Ratios[a]				
	Cost	QALYs	Cost	QALYs	Cost	QALYs	Cost	QALYs	N vs I	N vs IS	N vs F	F vs I	F vs IS
100% full compliance	$15,497	14.37	$16,297	14.59	$17,519	14.81	$17,131	14.89	$3167	$2762	N[b]	$4595	$5554
Initial compliance rate for N equal to base case I	$15,348	14.32	$16,061	14.40	$16,998	14.58	$16,566	14.56	$5096	$3300	$16,615[c]	$6346	$5206
Compliance rates I equal to base case N	$15,354	14.33	$16,061	14.40	$16,998	14.58	$16,669	14.64	$4188	$2544	N[b]	$6576	$5206
100% full compliance for I only	$15,497	14.37	$16,297	14.59	$16,998	14.58	$16,669	14.64	$4357	$6764	N[b]	$7148	I[d]
Prophylaxis treatment N equal to base case I	$15,348	14.32	$15,832	14.40	$16,998	14.58	$16,171	14.64	$2572	$1436	N[b]	$6346	$6478
26% depression recurrence rate on maintenance treatment	$15,294	14.34	$16,031	14.41	$16,999	14.58	$16,669	14.64	$4513	$2801	N[b]	$6973	$5776
40% depression recurrence rate for dropouts from maintenance treatment	$15,447	14.29	$16,192	14.40	$17,215	14.58	$16,850	14.64	$3962	$2709	N[b]	$6126	$5767
26% depression recurrence rate on maintenance treatment and 40% depression recurrence rate for dropouts from maintenance treatment	$15,381	14.31	$16,157	14.41	$17,215	14.58	$16,850	14.64	$4457	$3017	N[b]	$6944	$6443

*All costs and QALYs are discounted to present value using a 5% rate.
[a]Incremental cost-utility ratio from the perspective of nefazodone or fluoxetine.
[b]Indicates that nefazodone is cost saving compared with fluoxetine.
[c]Incremental cost-utility ratio from the perspective of fluoxetine.
[d]Indicates that imipramine step approach is cost saving compared with fluoxetine.

Assuming 100% compliance with imipramine and keeping base case compliance rates for nefazodone resulted in a cost-effectiveness ratio of $4357 per QALY gained. The cost-effectiveness ratio comparing the step approach with nefazodone was $6764 per QALY gained. Under this scenario, fluoxetine compared with imipramine resulted in a cost-effectiveness ratio of $7148 per QALY gained. Fluoxetine was now $701 more expensive than the step approach and produced 0.01 fewer QALYs. In a worst-case scenario, with 100% compliance for imipramine and nefazodone compliance rates equal to those of imipramine in the base case, the cost-utility ratio for nefazodone was $5841 per QALY gained. The cost-effectiveness ratio comparing fluoxetine with imipramine was $10,976 per QALY gained. In this case, the step approach had lower estimated medical costs ($16,297 vs. $16,566) and produced more QALYs (14.59 vs. 14.55) compared with nefazodone. Findings were comparable for fluoxetine.

Maintenance treatment. A sensitivity analysis was performed by making the maintenance treatment probabilities of nefazodone equal to those of the imipramine group (Table 4). For this scenario, the cost-effectiveness ratio of nefazodone compared with imipramine was $2572 per QALY gained. The cost-effectiveness ratio comparing nefazodone and the imipramine step approach was $1436 per QALY gained. Compared with the base case fluoxetine estimates, nefazodone costs $827 less than fluoxetine and yields only 0.06 more QALYs.

Since there are few comparative data on depression recurrence rates while on maintenance treatment, we performed sensitivity analyses by assuming a rate of 26% regardless of medication. The cost-effectiveness ratio comparing nefazodone with imipramine was now $4513 per QALY gained, and compared with the imipramine step approach was $2801 per QALY gained (Table 4). The comparison between fluoxetine and imipramine yielded a cost-effectiveness ratio of $6973 per QALY gained. When fluoxetine was compared with the imipramine step approach, the cost-effectiveness ratio was $5776 per QALY gained.

We also performed the economic analysis by assuming a 40% rate of recurrence of major depression for dropouts from maintenance treatment for all treatments. The cost-effectiveness ratio comparing nefazodone and imipramine treatment was now $3962 per QALY gained and comparing fluoxetine and imipramine treatment was $6126 per QALY gained (Table 4). No real substantive changes in the cost-effectiveness ratios comparing the newer antidepressants with the imipramine step approach were observed.

Finally, we combined the previous two sensitivity analyses and recalculated the cost-effectiveness ratios (Table 4). The comparison between nefazodone and imipramine yielded a cost-effectiveness ratio of $4457 per QALY gained. When nefazodone was compared with the imipramine step approach, the cost-effectiveness ratio was $3017 per QALY gained. The cost-effectiveness ratio

comparing fluoxetine with imipramine was now $6944 per QALY gained, and compared with the imipramine step approach was $6443 per QALY gained.

DISCUSSION

This study estimated the medical costs and QALYs of patients treated for major depression with either nefazodone, imipramine, or fluoxetine. We also evaluated the cost-effectiveness of nefazodone or fluoxetine compared with an approach where access to newer antidepressants is restricted to patients failing initial TCA therapy. The cost-effectiveness analysis was conducted from the perspective of an MCO; clinical decision analysis techniques were used to estimate the lifetime direct medical costs and health consequences of antidepressant treatment. The results demonstrate that nefazodone is cost-effective compared with imipramine treatment and the imipramine step approach. It was also shown that fluoxetine is cost-effective compared with imipramine treatment and the step approach. Nefazodone produced slightly lower lifetime medical costs and slightly more QALYs than fluoxetine.

The findings have implications for formulary policies in MCOs. We found that both nefazodone and fluoxetine were cost-effective compared with the step approach to antidepressant treatment. The cost-effectiveness ratio was $2555 per QALY gained for nefazodone, and sensitivity analyses did not substantially change these findings. The cost-effectiveness ratio was $5206 per QALY gained for fluoxetine compared with the step approach. MCOs may not achieve the medical cost savings assumed under a restrictive policy on access to SSRIs and other newer antidepressants. The model suggests that the outcomes of patients may be worse under the step approach. More recent prospectively collected data demonstrate no significant difference in depression and health status outcomes but comparable medical costs between fluoxetine and a TCA step approach.[43]

This cost-effectiveness analysis was based on a model for estimating the costs and health outcomes of different antidepressants. A modeling study was conducted rather than a prospective economic study because it allowed estimation of costs and outcomes over longer time periods. It also provided estimates of the cost-effectiveness of nefazodone and fluoxetine more quickly than primary data collection of medical resource use, costs, and health outcomes. Although modeling studies can be used to estimate the cost-effectiveness of new therapies, there is always some uncertainty to modeling. This uncertainty is exacerbated when there are few data on the long-term treatment of depression and few direct comparisons between the alternative antidepressant therapies in primary care practice.

Decision model–based economic analyses provide acceptable estimates of the costs and outcomes of new medical treatments. However, decision models and their findings are only as good as their underlying assumptions and the quality of the data used to estimate key model parameters.[36,38,40] Decision analyses may be subject to bias since there are a number of simplifying assumptions that must be made to construct a model. There are also limitations associated with using data from randomized clinical trials because of differences between clinical trial and primary care populations.[34] Models using clinical trial data quite likely overestimate treatment response rates and compliance rates. Until more prospective data on outcomes and medical costs in primary care settings become available, we are dependent on data from randomized clinical trials for many model parameters. Sensitivity analyses that test model assumptions can help us understand the implications of various model assumptions. We performed extensive sensitivity analyses, concentrating on those model parameters about which we were least certain, such as compliance rates for different antidepressants.

We modified different model parameters to examine effects on the medical costs and QALYs for nefazodone and the comparison antidepressants. These sensitivity analyses confirmed that the cost-effectiveness of nefazodone ranged from $2572 to $5841 per QALY gained compared with imipramine and that the cost-effectiveness of fluoxetine ranged from $4595 to $7148 per QALY gained compared with imipramine. When compared with the step approach, nefazodone had cost-effectiveness ratios ranging from $1436 to $6764 per QALY gained and fluoxetine had cost-effectiveness ratios from $5206 to $5554 per QALY gained. The analyses indicated that in almost all cases, nefazodone was cost saving when compared with fluoxetine. The worst cost-effectiveness ratio was $5841 per QALY gained when very conservative assumptions about nefazodone therapy were compared with imipramine treatment. For this case, the cost-effectiveness ratio for fluoxetine was $10,976 per QALY gained. These may not be entirely reasonable assumptions, since for this analysis nefazodone was assumed to have the same compliance rate as imipramine. Evidence suggests that, compared with imipramine, fewer nefazodone patients discontinue treatment in clinical trials because of adverse effects and/or lack of efficacy.[26]

Overall, the cost-effectiveness analyses suggest that nefazodone and fluoxetine are cost-effective compared with TCAs. All of the cost-effectiveness ratios are less than the $20,000 (Canadian dollars) per QALY gained criterion suggested by Laupacis et al.[61] to be supportive of immediate adoption into the health care system. The cost-effectiveness ratios are lower than comparable ratios for medical treatment for chronic diseases.[59] For example, the cost-effectiveness of antihypertensive therapy ranges from about $16,000 to $33,000 per QALY gained. Therefore, the newer antidepressants demonstrate cost-effec-

tiveness ratios that are comparable with or better than those estimated for antihypertensive therapy.

Jonsson and Bebbington[32] compared the cost-effectiveness of paroxetine and imipramine in the acute treatment of major depression. Their study estimated costs over a 12-month period and examined costs per successfully treated case based on clinical trial data. The definition of successful treatment was the number of patients discontinuing the trial for lack of efficacy or for adverse events subtracted from the total number of cases. They found that paroxetine was cost saving compared with imipramine. Marginal cost-effectiveness ratios ranged from $5 to $1257 when assumptions about efficacy were varied from 50% to 60%.[32] Our analysis differs in that we evaluated medical costs and outcomes over a longer duration, used QALYs based on patient-derived utilities to assess outcome, and incorporated assumptions about long-term compliance to therapy and depression recurrence rates. Despite these differences, the two studies estimated comparable cost-effectiveness ratios. The importance of assumptions regarding compliance with antidepressant therapy was also confirmed in both models.

These cost-effectiveness findings differ from those of an earlier model comparing the costs and QALYs of imipramine, nefazodone, and fluoxetine in the Ontario health care system.[34] The Canadian model estimated that nefazodone and fluoxetine were cost saving compared with imipramine treatment for depression. Cost-effectiveness ratios comparing nefazodone with imipramine ranged from cost-saving to $12,995 per QALY gained,[34] while the U.S. model ratios ranged from $2572 to $5841 per QALY gained. The differences in findings are explained by differences in model parameters relating to medical resource use (especially hospitalization), compliance rates, and depression recurrence rates. Despite the differences in the two clinical decision models, the findings are supportive of the cost-effectiveness of nefazodone and fluoxetine.

The cost-effectiveness ratios for nefazodone in this study are comparable with those from a recent analysis of quality improvement of antidepressant care in primary care practice.[62] Sturm and Wells[62] used a simulation model based on Medical Outcome Study data on services and outcomes to evaluate various changes in the health care system. Cost-effectiveness ratios for improving care for depression ranged from $870 to $4610. Their model included only acute care costs and outcomes and did not allow for continuation antidepressant treatment.

Clinical decision models are difficult to fully validate.[40] Our model estimated first-year medical costs between $1069 and $1171 depending on antidepressant treatment. Sturm and Wells,[62] using Medical Outcome Study data, estimated annual costs of depression treatment in primary care patients between $1070 and $1980. Simon et al.[63] found that the average annual cost of depression and anxiety in an MCO was $1098 to $2390. More recently, Simon and colleagues[43] prospectively collected mental health care and other medical care use and cost data for patients treated with TCAs or fluoxetine in an MCO. Six-month medical costs ranged from $1967 to $2361.[43] The medical costs estimated in our decision model are comparable with those reported by other studies[62,63] or within the range of existing studies,[43,62–64] which provides some support for the validity of the model.

Several caveats need to be mentioned. First, no attention is paid to indirect costs in the model, that is, the societal impact of lost productivity and absenteeism. Although these costs are important from the societal perspective and are estimated to be significant,[7] consideration of indirect costs is not relevant from the MCO perspective. However, the addition of productivity costs is not likely to modify the overall conclusions, since lost productivity costs are directly associated with episodes of depression and the impact of depression on quality of life.[4–6] Gold et al.[65] recommend incorporating productivity costs associated with morbidity into the estimate of QALYs in cost-effectiveness analyses, as was done in the current study. Second, we made an assumption as to the targeted patient population, that is, 30-year-old women with one previous depressive episode, mainly to simplify the estimation of mortality from life tables. To the extent that there are differences in treatment outcomes and compliance behavior between men and women, and younger and older patients with depression, these findings may change. Differences in practice patterns and health care systems may also influence the estimation of medical costs in the model. Given the available data, it is difficult to estimate the extent of change in cost-effectiveness attributable to our population assumptions if the model was estimated based on other population assumptions. However, the focus of the economic analysis is on the incremental cost-effectiveness ratios, given the model assumptions.

COMMENT

New pharmacotherapies for depression need to be evaluated for their efficacy, safety, and cost-effectiveness so that health care decision-makers and physicians can determine the value of new therapies compared with existing treatments. Cost-effectiveness analyses provide estimates of the health care costs and outcomes of practice patterns for treating major depression in primary care. Some health systems and MCOs may discourage the use of newer antidepressants, such as nefazodone, fluoxetine, or venlafaxine, based on pharmacy acquisition price alone. In our model, when the long-term costs and effects are estimated, nefazodone and fluoxetine treatments were found to be cost-effective compared with both imipramine alone and a step approach where access to newer antidepressants is restricted. Decisions about antidepressant therapies require attention to clinical efficacy and safety

and all relevant health care costs, not just price of the drug. Nefazodone and fluoxetine have clinical efficacy comparable with TCAs and much better side effect profiles compared with the TCAs. Patients may benefit from nefazodone or fluoxetine treatment and, on the basis of this clinical decision model, there also may be savings in health care costs associated with nefazodone compared with fluoxetine treatment of major depression.

Drug names: fluoxetine (Prozac), imipramine (Tofranil and others), nefazodone (Serzone), paroxetine (Paxil), venlafaxine (Effexor).

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Appendix 1. Estimated Annual Use of Medical Services by Outcome and Compliance Category for U.S. Managed Care Organization Antidepressant Treatment Model*

	Remission		Episode, FC		Episode, PC		Episode, MC		Episode, Dropout	
Medical Service	%	Number	%	Number	%	Number	%	Number	%	Number
Hospitalization										
General[a]	0	0 days	2	4 days	2	4 days	2	4 days	2	4 days
Psychiatric[b]	0	0 days	2.5	6 days	1.5	6 days	1.5	6 days	1.5	6 days
Electroconvulsive therapy[c]	0	0 sessions	1	12 sessions	1	12 sessions	1.5	12 sessions	0	0 sessions
Psychiatrist										
Outpatient visit	0	0 visits	25	7 visits	15	3 visits	10	2 visits	0	0 visits
Psychiatric interview	0	0 visits	25	1 visit	15	1 visit	10	1 visit	0	0 visits
Primary care physician										
Outpatient visit[d]	100	4 visits	100	4 visits	100	3 visits	100	2 visits	100	2 visits
Psychological counseling										
Outpatient visit	0	0 visits	20	7 visits	10	5 visits	10	1 visit	0	0 visits
Laboratory[e]	0	0 tests	100	1 test	100	1 test	100	1 test	100	1 test
Antidepressants[f]	0	0 days	100	260 days	100	194 days	100	138 days	100	42 days

	Prophylaxis, No Episode		Prophylaxis, Episode		Prophylaxis, Dropout		Treatment-Resistant	
Medical Service	%	Number	%	Number	%	Number	%	Number
Hospitalization								
General[a]	0	0 days	2	4 days	0	0 days	0	0 days
Psychiatric[b]	0	0 days	2.5	6 days	0	0 days	50	6 days
Electroconvulsive therapy[c]	0	0 sessions	1	12 sessions	0	0 sessions	50	12 sessions
Psychiatrists								
Outpatient visit	20	4 visits	25	8 visits	20	1.33 visits	10	12 visits
Psychiatric interview	0	0 visits	25	1 visit	0	0 visits	0	0 visits
Primary care physician								
Outpatient visit[d]	100	3 visits	100	4.75 visits	100	1 visit	0	0 visits
Psychological counseling								
Outpatient visit	10	2 visits	20	7.5 visits	10	0.67 visits	50	7 visits
Laboratory[e]	0	0 tests	100	1 test	0	0 tests	10	1 test
Antidepressants[f]	100	365 days	100	365 days	100	120 days	10	365 days

*Abbreviations: FC = full compliance; MC = minimal compliance; PC = partial compliance.
[a]For each hospitalization, there are 1 psychiatrist inpatient consult and 3 primary care physician inpatient visits.
[b]For each hospitalization, there are 1 psychiatrist inpatient consult and 5 psychiatrist inpatient follow-up visits.
[c]Electroconvulsive therapy includes 12 psychiatrist visits.
[d]Initial outpatient visit is for new patient, with remainder outpatient visits for established patients.
[e]Laboratory includes thyroid panel, SMA-20, CBC, and for imipramine-treated patients, one imipramine blood level per year.
[f]For antidepressant drugs, number of days of treatment are multiplied by daily price of specific antidepressant.

Appendix 2. Medical Resource Prices for Clinical Decision Model of Antidepressant Treatment in Managed Care Organizations

Service	Price ($)[a]
Hospital[b]	
Inpatient day: general hospital	$721
Inpatient day: psychiatric hospital	748
Session: electroconvulsive therapy	200
Emergency room visit	170
Physician[c]	
Psychiatrist	
Inpatient visit: initial consult	$156
Inpatient visit: subsequent care	72
Electroconvulsive therapy	193
Outpatient visit: psychiatric interview	155
Outpatient visit: established patient	52
Primary care physician	
Inpatient visit: initial care	$149
Inpatient visit: subsequent care	69
Outpatient visit: established patient	49
Psychological counseling[c]	
Outpatient visit: individual psychotherapy	$100
Laboratory[c]	
Thyroid panel	$91
SMA-20	33
CBC	25
Imipramine blood level	51
Medications[d]	
Nefazodone (300 mg/d)	$1.56
Fluoxetine (20 mg/d)	1.84
Imipramine (150 mg/d)	0.38
Trazodone (100 mg/d)	0.65

[a]All prices rounded to nearest 1994 U.S. dollar.
[b] Source: Managed care organizations, 1994, unpublished data; Health Care Financing Administration. Payment for Part B Medical and Other Health Services. Federal Register. December 1993; Revicki DA, Palmer CS, Phillips SD, et al. Acute medical costs of fluoxetine versus tricyclic antidepressants: a prospective multicenter study of drug overdoses. Pharmacoeconomics 1997;11:48–55.
[c]Source: Managed care organizations, 1994, unpublished data; Health Care Financing Administration. Payment for Part B Medical and Other Health Services. Federal Register. December 1993.
[d]Source: Managed care organizations, 1994, unpublished data; Red Book Pharmacy's Fundamental Release. Montvale, NJ: Medical Economics Data Production Company, 1994; Data on file, 1995, Bristol-Myers Squibb, Princeton, N.J.

Appendix 3. Estimated Annual Medical Costs and Quality-Adjusted Life Years (QALYs) for U.S. Managed Care Organizations Antidepressant Treatment Model*

Outcome/Event	Annual Cost[a]	Annual QALY
Remission/recovery	$ 198	0.8950
Nefazodone		
FC, episode	$1628	0.7769
PC, episode	1253	0.7359
MC, episode	1078	0.6720
Dropout, episode	822	0.5872
FC, prophylaxis, no episode	1119	0.8750
Dropout, prophylaxis, no episode	600	0.8750
FC, prophylaxis, episode	1823	0.7966
Fluoxetine		
FC, episode	$1725	0.7661
PC, episode	1326	0.7314
MC, episode	1130	0.6703
Dropout, episode	837	0.5863
FC, prophylaxis, no episode	1255	0.8590
Dropout, prophylaxis, no episode	645	0.8590
FC, prophylaxis, episode	1954	0.7804
Imipramine		
FC, episode	$1470	0.7281
PC, episode	1124	0.7142
MC, episode	966	0.6607
Dropout, episode	772	0.5815
FC, prophylaxis, no episode	739	0.7970
Dropout, prophylaxis, no episode	473	0.7970
FC, prophylaxis, episode	1570	0.7242
Step imipramine to nefazodone		
FC, episode	$1746	0.7579
PC, episode	1371	0.7169
MC, episode	1196	0.6530
Dropout, episode	940	0.5682
Death, natural causes	$ 99	0.4476
Suicide	$2098	0.3493
Treatment-resistant depression	$7417	0.6887

*Abbreviations: FC = full compliance; MC = minimal compliance; PC = partial compliance.
[a]All costs rounded to nearest 1994 U.S. dollar.