A Budget-Impact and Cost-Effectiveness Model
for Second-Line Treatment of Major Depression

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ABSTRACT

BACKGROUND: Depressed patients who initially fail to achieve remission when placed on a selective serotonin reuptake inhibitor (SSRI) may require a second treatment.

OBJECTIVE: The purpose of this study was to evaluate the effectiveness, cost, cost-effectiveness, and budget impact of second-line pharmacologic treatment for major depressive disorder (MDD).

METHODS: A cost-effectiveness analysis was conducted to evaluate second-line therapies (citalopram, escitalopram, fluoxetine, paroxetine, paroxetine controlled release [CR], sertraline, and venlafaxine extended release [XR]) for the treatment of depression. Effectiveness data were obtained from published clinical studies. The primary outcome was remission defined as a score of 7 or less on the Hamilton Rating Scale for Depression (HAM-D) or a score of 10 or less on the Montgomery-Asberg Depression Rating Scale (MADRS) depression rating scales. The wholesale acquisition cost (WAC) for medications and medical treatment costs for depression were included. The perspective was derived from a managed care organization (MCO) with 500,000 members, a 1.9% annual incidence of depression, and treatment duration of 6 months. Assumptions included: second-line treatment is not as effective as first-line treatment, WAC price reflects MCO costs, and side effects were identical. Sensitivity analyses were conducted to determine variables that influenced the results.

RESULTS: Second-line remission rates were 20.4% for venlafaxine XR, 16.9% for sertraline, 16.4% for escitalopram, 15.1% for generic SSRIs (weighted average), and 13.6% for paroxetine CR. Pharmacy costs ranged from $163 for generic SSRIs to $319 for venlafaxine XR. Total cost per patient achieving remission was $14,275 for venlafaxine XR, followed by $16,100 for escitalopram. The incremental cost-effectiveness ratio (ICER) for venlafaxine XR compared with generic SSRIs was $2,073 per patient achieving remission, followed by escitalopram with an ICER of $3,566. The model was most sensitive to nonpharmacy costs.

CONCLUSION: This analysis suggests that second-line treatment of depression with venlafaxine XR may result in more patients achieving remission, with an ICER that is favorable to other therapies.

KEYWORDS: SSRI, SNRI (serotonin norepinephrine reuptake inhibitor), Antidepressants, Cost-effectiveness model, Major depressive disorder, Budget-impact model, Venlafaxine extended release (XR), Managed care

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As addressed in the preceding article, major depressive disorder (MDD) is a significant health problem with economic implications for patients, health insurance companies and other health care payers, and employers. Use of second-generation antidepressants has become the de facto standard for the treatment of MDD. Expenditures for antidepressants represented the third-largest drug therapy class in 2000.[1] Estimates of the economic burden of depression range from $52 billion in 1990 to $83 billion in 2000.[2,3]

The burden of depression includes not only the direct medical costs of treatment, but also the social and intangible costs of missed worked, lower productivity, and decreased quality of life.[4-7] The risk of death is also much higher in patients with depression.[8]

■ Antidepressant Therapy

Assessing the Cost-Effectiveness of Antidepressant Therapy

A number of issues arise when assessing the cost-effectiveness of antidepressant therapy. Among these issues are which agents to assess, how to measure their effectiveness, the duration of clinical trials versus the duration of analysis, which costs to consider, the perspective of the analysis, consideration of tolerability issues, and a multitude of clinical trial design options. Although it is beyond the scope of this article to discuss all of these issues in detail, it is important to consider some of them in the context of cost-effectiveness analysis.

Several depression rating scales have been developed, such as the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory, and the Clinical Global Impression-Severity (CGI-S), that assess the clinical efficacy of various treatments for MDD. Although many rating scales exist for the purpose of evaluating antidepressant therapy, the vast majority of clinical trials have incorporated either the HAM-D or MADRS instruments. The HAM-D was first published in 1960 to assess the effectiveness of first-generation antidepressants.[9] A published review of the HAM-D concluded that the instrument has psychometric properties that are adequate and consistently meet established criteria for validity and reliability.[10] The MADRS instrument was first published in 1979 and is a commonly used instrument to assess the efficacy of antidepressants.[11] Both instruments (HAM-D and MADRS) have been widely used in clinical trials to evaluate the efficacy of antidepressant therapy.

Defining Response and Remission

The goal of depression treatment is remission—the virtual absence of depressive symptoms. Remission is associated with improved function and a more optimistic prognosis than is a response without remission.[12] Further, achieving remission

has been associated with a reduction in the rate of relapse and improved psychological functioning compared with patients with partial response.[13-16] Studies indicate that compared with patients who achieve remission, those with incomplete resolution of symptoms are 3 to 5 times more likely to relapse.[15,17]

Consensus has suggested that values of 7 or less on the HAM-D are indicative of clinical remission.[18,19] For the MADRS instrument, cut-off values of 9 or less have been found to be approximately 1 standard deviation from the mean of nondepressed patients,[20] with various other cut-off values (9-12) having been used.[21] Consequently, many clinicians have come to accept that values of 10 or less are likely to indicate remission.

Evaluating Antidepressant Therapy Effectiveness

Several meta-analyses and evidence reviews have been conducted to evaluate the effectiveness of selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor (SNRI) products.[22,23] Most recently, RTI International conducted an evaluation of second-generation antidepressants and their comparative effectiveness for the treatment of depression.[24,25] The overall conclusion of the report was that there was little evidence to indicate that SSRIs and SNRIs are clinically different from one another despite evidence of statistical differences.[25] The results suggested that escitalopram improved response over citalopram (relative risk [RR], 1.14; 95% confidence interval [CI], 1.04-1.26), sertraline improved response over fluoxetine (RR, 1.11; 95% CI, 1.01-1.21), and venlafaxine extended release (XR) improved response over fluoxetine (RR, 1.12; 95% CI, 1.01-1.24) as well as having higher rates of remission (odds ratio [OR], 1.42; 95% CI, 1.17-1.73).[24] The authors commented that these differences represented a relatively small difference on the HAM-D instrument and were likely to be clinically insignificant. Another aspect of the RTI report was that no overall analysis was reported, which is unfortunate given the substantial amount of data collected. In addition, the report focused on studies that used identical instruments, such as the HAM-D, to evaluate remission rates. This analytical decision prevents indirect comparisons between agents that might provide valuable information about their effectiveness.

One of the major difficulties of conducting such meta-analyses is that published reports sometimes fail to contain sufficient information to properly evaluate the study. For example, a proper meta-analysis will require the mean and standard deviation of the treatment groups both at baseline and at the end of the study. It is not uncommon for authors to report only the standard deviation at baseline but not at the end of the study. Also, many authors will report only the change from baseline score and not the score at the end of the study. Another complicating issue when comparing studies is that some analyses will not report means, but only percentages of patients achieving some threshold. As mentioned earlier, some consensus exists on values of the HAM-D and MADRS that

constitute remission, but not all studies use identical cut-off points. Therefore, studies that fail to report an end-of-study mean and a standard deviation cannot be used if a different threshold for remission is used.

Previous Economic Studies of Antidepressant Therapy

A recent review of the literature evaluated the economics of antidepressants and various other therapies for the treatment of MDD.[26] This review identified 18 manuscripts that evaluated the cost-effectiveness of antidepressant therapies, most of which were models. None of the analyses based on clinical trials compared second-generation antidepressants, although some economic models have compared SSRIs as a group to tricyclic antidepressants (TCAs). Results from the models evaluating these classes of antidepressants were mixed, to some extent depending on how side effects and adverse effects were taken into consideration. For example, a Canadian study reported no advantage of SSRIs versus TCAs with respect to cost-effectiveness.[27] A number of other studies have suggested that SSRIs are cost-effective relative to TCAs.[28-29]

Other models have compared specific SSRIs and SNRIs. All of these models either stated explicitly or assumed that treatment was for first-line therapy. Many models included options for a failed response to the first-line agent, but there was heterogeneity in the structure of the models with respect to second-line treatment options. Another important issue to highlight with economic models is the outcome of interest. While all studies have used some measure of patient-reported symptoms, the operationalization of these severity scales is not necessarily consistent. Some models have used response, while others have used remission as the outcome of interest. Other studies have converted performance on the HAM-D or MADRS instruments into symptom-free days (SFDs) or depression-free days (DFDs), which were essentially equivalent. Many of the economic studies reported to date derive estimates of clinical efficacy from a single study, which can be problematic if the clinical trial population does not reflect the overall population being treated. A brief summary of the models and their findings is provided in some detail in the following section.

■ Summary of Economic Models

Wade et al. compared citalopram and escitalopram using a 6-month probabilistic model from a United Kingdom (U.K.) perspective.[30] The study used a 6-month time horizon, and the measure of effectiveness was remission, defined as a MADRS score of 12 or less without switching medications. The study found that escitalopram was more cost-effective than citalopram, with the overall remission rate for escitalopram being approximately 10% greater than citalopram while costs were about 16% lower for escitalopram. Using the Monte Carlo sensitivity analysis of 10,000 iterations, more than 99% of the cases were situations in which escitalopram was a dominant therapy

(less cost and more effective). It should be noted that the prices of escitalopram and citalopram in the U.K. were identical; therefore, cost differences were driven by decreased utilization of nondrug health care resources for escitalopram relative to citalopram.

In another study, Demyttenaeyre et al. reported on the cost-effectiveness of citalopram, escitalopram, and venlafaxine using a 2-stage model with a 6-month time horizon.[31] The study was evaluated from the Belgium Insurance Scheme as well as from a societal perspective. The first stage of the model assumed that patients who did not have a suicide attempt were treated with antidepressants and either achieved remission or could be switched to another agent or have the initial antidepressant dose titrated. Patients who had a suicide attempt were entered into a different model whereby treatment options included switching therapies, augmentation, or titration. Clinical evidence for the model was based on 3 clinical trials comparing 2 of 3 agents directly (citalopram to escitalopram, escitalopram to venlafaxine XR). It was found that escitalopram was more effective and less costly than citalopram. Remission rates were 52.8% for escitalopram versus 43.5% for citalopram. The societal cost of generic citalopram was €0.85 (euros) for 20 mg per day; escitalopram was €1.14 for 10 mg per day. Results from the Monte Carlo sensitivity analysis found that in 93.5% of the cases, escitalopram was dominant when compared with citalopram. In contrast, the comparison with venlafaxine XR was equivocal. Clinical efficacy rates were nearly identical between the 2 agents (escitalopram = 69.9%, venlafaxine XR = 69.7%). Results from the Monte Carlo sensitivity analysis suggested that escitalopram was more cost-effective than venlafaxine XR in approximately 61% of the cases.[31] This result appears to be due to differences in medication costs, with venlafaxine being slightly more expensive than escitalopram.

Another study comparing citalopram with escitalopram was conducted by Hemels et al.[32] This analysis was conducted from an Austrian societal and Social Healthcare Insurance System perspective using a 6-month time frame. Similar to previous models, the primary outcome of interest was remission of depression symptoms, and response was defined as a 50% reduction in depression symptoms from baseline. Clinical efficacy was derived from clinical trials including both agents. Because the costs of the medications were nearly identical, results from the model were driven by statistical differences in clinical efficacy. Again, escitalopram was found to be a dominant strategy regardless of the perspective taken. One-way sensitivity analyses suggested that the results were consistent across the range of parameters used in the model.

Kulp et al. used a Markov model to compare escitalopram with venlafaxine XR for first-line treatment of depression from a German health insurance perspective.[33] The model included 3 outcomes: response (greater than 50% reduction from baseline), partial response (25% to 50% reduction from baseline), or no response. Clinical efficacy was derived from a single randomized clinical trial comparing the 2 agents. For escitalopram, 77.4% of subjects were considered responders to therapy compared with 79.6% for venlafaxine XR. Cost-effectiveness of the respective therapies was expressed in terms of proportion of patients responding to therapy. Drug costs were based on defined daily doses as supplied by IMS Health Inc. and were €1.30 for escitalopram and €1.81 for venlafaxine XR. The duration of the study was 70 days. The results of the model suggested that the incremental cost-effectiveness of using venlafaxine XR was €7,446 if general practitioners treated patients.

Similarly, Fernandez et al. reported on the cost-effectiveness of escitalopram relative to venlafaxine XR based on the multicenter and multicountry clinical trial used in the Kulp et al. analysis.[34] However, this analysis was slightly different because the outcome of interest was quality of life as measured by the EuroQOL (quality of life) questionnaire (EQ-5D). Health care resource use was also captured, and health care costs were used from 6 of the 8 countries represented in the study, which was conducted from a societal perspective. No statistically significant difference between the 2 treatment groups was found with respect to EQ-5D scores. Health care resource use varied by the type of health care provider evaluated, but there was no clearly consistent trend or difference between escitalopram or venlafaxine XR. Likewise, there was no significant difference in total health care costs between the 2 groups. To simulate cost-effectiveness, a bootstrap sampling program was run 10,000 times. The results found that escitalopram was less costly in the majority of cases, but there was no clear difference in quality of life.

In another model evaluating escitalopram, Sullivan et al. constructed a 2-stage model of the treatment of depression that incorporated side effects of the various SSRI products on the market in the United States.[35] The model included patented and generic SSRI products with data on adverse events derived from the literature or product package inserts. The time frame of the model was 6 months, and data were derived from a managed care organization (MCO) perspective. The authors valued the costs of adverse events at more than $5,000 based on a previously reported study.[36] The model used quality-adjusted life-years (QALYs) as the primary outcome of interest, adjusting QALY values downward in the presence of adverse events. In this model, escitalopram was deemed to be the least costly ($3,891) and most effective (0.34) compared with citalopram, generic fluoxetine, venlafaxine XR, sertraline, generic paroxetine, paroxetine controlled release (CR), or venlafaxine. However, CIs for cost and effect were overlapping across all agents. The authors reported that in the analysis comparing escitalopram with fluoxetine, more than 99% of the cases from a simulation of 10,000 were below the $50,000-per-QALY threshold that is commonly used to define health technologies as cost-effective.

Using a clinical trial framework, Revicki et al. evaluated the

cost-effectiveness of pharmacotherapy (paroxetine or bupropion) or cognitive behavior therapy with community referral for major depression in women receiving care at public health or social service facilities over a 12-month time frame in the Washington, DC, metropolitan area.[37] The primary outcome of interest was QALYs, which were estimated from DFDs. To determine the number of DFDs over the course of the study, the following algorithm was used: HAM-D score of 7 or less = 1 DFD; HAM-D score of 8 to 21 = proportional weight to DFD; HAM-D of 22 or greater = 0 DFD. DFDs were then converted to QALYs. Health care resource use was obtained from patient charts for behavioral therapy and patient self-reports using structured telephone interviews. Costs of medical services were based on a Maryland Medicaid program fee schedule, and medication costs were based on the lowest published average wholesale price (AWP). The study found that pharmacotherapy was more effective than community referral after 12 months. The cost per QALY was $30,023 for pharmacotherapy and $37,568 for cognitive behavior therapy. Results were not presented separately for paroxetine and bupropion.

Another model compared 3 groups of antidepressants with respect to cost-effectiveness.[38] In this model, SSRIs consisting of fluoxetine, paroxetine, and fluvoxamine were compared with SNRIs (venlafaxine) and TCAs (amitriptyline). The perspective of the model was derived from the U.K. National Health System with a 6-month time horizon. An expert panel of 3 general practitioners and 2 psychiatrists assisted in the development of the decision model and provided estimates of probabilities for decision nodes where clinical evidence was not available. Clinical efficacy was obtained from a meta-analysis of clinical trials for SSRIs and venlafaxine, as well as from a single study for amitriptyline that was compared with a meta-analysis of TCA studies. The clinical parameters of interest were remission, which was defined as a score of 7 or less on the HAM-D instrument. Remission rates were also converted into SFDs, but the exact algorithm was not provided. Overall remission rates were 45% for venlafaxine, 35% for SSRIs, and 24% for amitriptyline. The low response rate for amitriptyline was due to a much higher drop-out rate than experienced with the other agents and to an intention-to-treat analysis that was used to calculate efficacy. The number of SFDs over the 6-month study period was estimated to be 61 for venlafaxine, 52 for SSRIs, and 44 for amitriptyline. The cost per SFD was £21.20 (British pounds) for venlafaxine, £26.12 for SSRIs, and £31.80 for amitriptyline.

In another analysis involving venlafaxine, Trivedi et al. developed a cost-effectiveness model based on a meta-analysis of 8 clinical trials involving venlafaxine and SSRIs (fluoxetine, paroxetine, and fluvoxamine).[39] The meta-analysis was the same one used by Lenox-Smith et al.[38] and was conducted from the perspective of a U.S. MCO with an 8-week time horizon. As with the previous economic model, this analysis evaluated the percentage of patients achieving remission and converted this

percentage into DFDs. The calculation of DFDs in this study was similar to the calculation of SFDs in other studies, whereby HAM-D scores of 7 or less = 1 DFD, values greater than 15 = 0 DFD, and scores between 8 and 14 were linearly weighted to equal values between 0 and 1 DFD. This model evaluated efficacy at 2-week intervals. Also, quality-adjusted days (QADs) were computed by assigning utility values to DFDs based on a previously published study.[40] Medication prices were based on 2002 AWPs. Where generic medications were available, the lowest-priced product was used and weighted by an estimate of the generic to brand use of the product. Nonpharmacy costs were limited to physician visits and laboratory costs. Results of the analysis found that venlafaxine had a higher percentage of patients achieving remission (44.9%) than did SSRIs (34.7%); venlafaxine also had more DFDs (22.82) than did SSRIs (18.61). The cost per patient achieving remission was $1,304 for venlafaxine and $1,515 for SSRIs. The cost per DFD was $25.66 for venlafaxine and $28.25 for SSRIs. A Monte Carlo simulation found the incremental cost-effectiveness ratio for SSRIs to have a 95% CI that ranged from $326 to $1,176, with a mean value of $586.

In summary, based on the studies conducted to date, SSRIs are cost-effective relative to TCAs for treatment of MDD. Also, many studies conclude that treatment with products producing fewer side effects or those more recently marketed appear to be cost-effective. However, a major limitation of these analyses is that they are largely based on select clinical trials that tended to enroll naïve patients with MDD. No known economic models have examined treatment-resistant MDD.

■ Budget Impact of Antidepressant Therapies

As mentioned previously, antidepressants represent the third-largest class of pharmaceuticals in the world in terms of dollar sales.[1] MCOs have recognized the need to appropriately manage these agents. Due to the availability of generic SSRI products, it makes sense for MCOs to encourage their first-line use because of their relatively similar efficacy but substantially lower costs. However, if patients fail initial therapy, choice of the second agent should incorporate such factors as reasons for failure, including side effects, nonresponse, and patient adherence. It is also important to keep in mind that the budget for antidepressants will include expenditures for the initial and treatment-resistant episodes. Because most health plans contain minimal data on reasons for failure of the initial agent, it becomes difficult to actively manage patients receiving antidepressant therapies. Health plans have limited alternatives for obtaining this data other than examining the pharmacy budget and estimating patient persistence to antidepressants by using pharmacy claims.

The Academy of Managed Care Pharmacy (AMCP) and the Foundation for Managed Care Pharmacy (FMCP) have written guidelines for formulary management explicitly stating that

health plans should evaluate pharmaceuticals from a cost-effectiveness and budget-impact perspective.[41] Budget-impact analysis is a necessary component because it gives health plans the ability to anticipate future expenditures for pharmaceuticals that are added to the formulary and to explore strategies that might assist in controlling expenditures and improving health outcomes of the enrolled population. For these reasons, dossiers submitted to health plans should incorporate a budget-impact assessment.

In an attempt to meet the real-world issues regarding the use of antidepressants, a cost-effectiveness and budget-impact model was constructed and is outlined in the following section. More specifically, the purpose of this model was to examine the cost-effectiveness of pharmacologic treatment options for treatment-resistant MDD and to assess the overall budget implications for an MCO.

■ Methods

Model Description

A budget-impact and decision-analysis model was constructed in Microsoft Excel. Products included in the model were generic SSRIs consisting of citalopram, fluoxetine, and paroxetine; escitalopram (Lexapro); paroxetine CR (Paxil CR); sertraline (Zoloft); and venlafaxine XR (Effexor XR). Even though it is off-patent, fluvoxamine was not included in the model due to lack of clinical studies (see the following section) and its infrequent use. Venlafaxine immediate release was also not included in the model because it is more expensive that venlafaxine XR and provides no additional advantages over the extended-release formulation. Duloxetine was also not included in the study because, at the time the study was conducted, no evidence concerning its efficacy in treatment-resistant depression had been published. The model used an MCO perspective with a 6-month time horizon.

Model Structure

The model first takes into account the proportion of patients who failed first-line therapy based on estimates from clinical trials. The model assumes that if patients failed first-line treatment, they continued on to second-line therapy. For those patients with an improvement (defined as response), they continued and an assessment of remission was determined.

For patients responding to therapy but not achieving remission, they entered 1 of 3 branches: switch, titrate, or augment therapy. The use of generic SSRIs was assumed for patients who switched or augmented therapies. For titration, it was assumed that dose escalation was conducted, whereby the cost of treatment was increased but the clinical probabilities remained constant. Patients who did not have an improvement were considered failures due to either a lack of efficacy or an adverse drug reaction (ADR). If patients had a lack of efficacy, treatment was switched, titrated, or augmented. For those

who failed due to an ADR, it was assumed that they switched therapies (to another generic SSRI).

Cost and Market Share

The model begins with information on the health plan organization and prevalence of treated depression. The base model assumed a health plan of 500,000 members with a prevalence rate of 1.9%. The model also assumed that the duration of treatment was 180 days and that medications would be supplied in 30-day increments. Consumer cost sharing was initially set at $10, $20, and $40 for first (generic), second (preferred branded SSRIs), and third tier (nonpreferred branded SSRIs), respectively. In this analysis, no agents were assigned into the third tier.

The model included the ability to alter various aspects of product use. Input parameters included the daily average consumption (commonly referred to as DACON); wholesale acquisition price (WAC); rebates, if any, expressed in terms of percentage off WAC; market share by product strength; and copayment tier. The model assumed that DACON for all products was constant and had a value of 1, and there was no rebate for any of the products. Medication prices were obtained from a Medispan data file (September 2005). The market share by strength was taken from data obtained from IMS Health Inc. (December 2004). A weighted price for each product was calculated to reflect the market share. For example, citalopram is marketed in 10-mg, 20-mg, and 40-mg strengths. From IMS Health, Inc. data, it was determined that the 10-mg strength comprised 6.5% of all citalopram sales, whereas the 20-mg and 40-mg strengths comprised 53.2% and 40.3% of the market, respectively. The WAC price for each strength of citalopram was $0.64, $0.62, and $0.67 for the 10-mg, 20-mg, and 40-mg strengths, respectively. Consequently, the price of citalopram was estimated to be $0.64. The net plan cost for each agent was calculated by multiplying the weight price by the days of treatment, but subtracting out patient copayments. Distributions of market share and price are shown in Table 1.

Generic SSRIs were assumed to be first-line treatment for MDD. The market share for first-line treatment was 20%, 40%, and 40% for citalopram, fluoxetine, and paroxetine, respectively. These market shares were also based on data from IMS Health Inc. If a patient failed initial treatment, the model assumed another agent such as a branded SSRI, a generic SSRI, or venlafaxine XR, which was then used. The respective market share for second-line use was 15% for citalopram, 15% for fluoxetine, 15% for escitalopram, 15% for paroxetine, 5% for paroxetine CR, 20% for sertraline, and 15% for venlafaxine XR. Thus, generic SSRIs accounted for 45% of second-line agents.

The base analysis was conducted by increasing the market share of venlafaxine XR from 15% to 20%; generic SSRIs would decrease by 3% and sertraline would decrease by 2%. The other products' market share would remain the same.

TABLE 1 Cost, Distribution by Market Share, and Weighted Cost for Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

Product	Strength (mg)	WAC ($)	% of Market by Strength	Weighted Price by Market Share ($)	Weighted Price ($)
Citalopram	10	0.64	6.5	0.04	0.64
Citalopram	20	0.62	53.2	0.33	
Citalopram	40	0.67	40.3	0.27	
Escitalopram	5	1.85	1.3	0.02	1.86
Escitalopram	10	1.85	61.9	1.15	
Escitalopram	20	1.89	36.8	0.70	
Fluoxetine generic	10	0.44	12.1	0.05	0.48
Fluoxetine generic	20	0.48	72.6	0.35	
Fluoxetine generic	40	0.48	15.3	0.07	
Paroxetine generic	10	1.97	15.6	0.31	2.08
Paroxetine generic	20	2.05	53.8	1.10	
Paroxetine generic	30	2.12	12.3	0.26	
Paroxetine generic	40	2.24	18.3	0.41	
Paroxetine CR	12.5	2.40	31.7	0.76	2.48
Paroxetine CR	25	2.50	54.0	1.35	
Paroxetine CR	37.5	2.58	14.4	0.37	
Sertraline	25	2.30	6.7	0.15	2.30
Sertraline	50	2.30	41.1	0.95	
Sertraline	100	2.30	52.2	1.20	
Venlafaxine XR	37.5	2.53	10.5	0.27	2.91
Venlafaxine XR	75	2.84	48.0	1.36	
Venlafaxine XR	150	3.09	41.5	1.28	
Weighted generic price					1.15

WAC=wholesale acquisition cost.

Rather than use expert panels to estimate nondrug medical care costs, such as physician visits, laboratory tests, and inpatient mental health care, the costs associated with remission, response, and treatment failure were based on an analysis of 1,814 persons enrolled in 10 antidepressant studies conducted by Group Health Cooperative in western Washington state.[42] Clinical response to antidepressant therapy was categorized in an identical manner as the economic model. Medical care costs were then estimated based on the end-of-study status with respect to clinical outcomes.

Clinical Evidence

Clinical evidence for this study came from published trials of the agents of interest. The following criteria were used to identify relevant studies: (1) randomized, comparative, double-blind, controlled clinical trials of SSRIs and SNRIs in the treatment of MDD that evaluated any of the following: citalopram, escitalo-

pram, fluoxetine, sertraline, paroxetine, and venlafaxine XR; (2) depression was assessed with either the HAM-D or MADRS instruments; (3) a duration of at least 8 weeks of therapy; (4) a sample size of greater than 30 patients per group; and (5) reported baseline mean and standard deviation as well as end-of-study mean and standard deviation. Studies were identified through searches of MEDLINE and PsycINFO databases using the following search strategies. First, studies involving the treatment of depression were selected and were limited to double-blind trials. Next, further restrictions were implemented to the medications of interest for this study (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine XR). For the PsycINFO database, searches were conducted using terms related to depression or major depression. Studies were limited to clinical trials and to the medications of interest. Finally, MEDLINE and PsycINFO results were compared and duplicates removed.

TABLE 2 — Remission, Response, and Discontinuation Rates for Initial Treatment of Depression

Product	Remission Rate (%)	Response Rate (%)	Discontinuation Rate (%)
Citalopram	35.6	61.3	4.0
Escitalopram	41.2	70.0	5.7
Fluoxetine	38.7	58.7	8.3
Paroxetine CR	32.2	60.0	8.1
Paroxetine generic	32.2	60.0	8.1
Sertraline	40.0	62.8	7.2
Venlafaxine	41.6	67.4	11.8

TABLE 3 — Remission and Response Rates for Treatment-Resistant Depression

Product	Remission Rate (%)	Response Rate (%)
Citalopram	15.1	25.9
Escitalopram	16.4	27.9
Fluoxetine	16.7	27.2
Paroxetine CR	13.6	25.4
Paroxetine generic	13.6	25.4
Sertraline	16.9	26.6
Venlafaxine	20.4	32.6

Clinical efficacy was determined by examining data for response and remission. Response was defined as a 50% or greater improvement from the baseline depression rating score. Remission was defined as a score of 7 or less for the HAM-D or 10 or less for the MADRS instruments. For generic medications, remission and response rates were weighted by market share, similar to medication pricing. The clinical evidence for paroxetine CR was based on studies including paroxetine and paroxetine CR. Studies of second-line treatment (treatment-resistant) for depression were less common, leading to relaxation of the inclusion and exclusion criteria. Treatment-resistant evaluations included both randomized-blinded and open-label studies.

Methods to Combine Clinical Studies

For each product of interest, data were summarized across all studies evaluating that specific agent by weighting the included studies by sample size. For those studies not reporting the percentage of patients who achieved remission or response, a normal distribution was used to estimate the proportion achieving these thresholds. Because of the lack of data for parox-

etine CR, it was assumed that estimates of clinical efficacy were similar to nonextended-release paroxetine.

Second-line response rates were estimated by adjusting downward response and remission rates from initial treatment trials. The amount of the adjustment was obtained from clinical studies that examined the use of each agent in treatment-resistant depression.

Discontinuation rates were also estimated from clinical trials. Similar to clinical efficacy rates, discontinuation rates were weighted by sample size to obtain a pooled estimate for each agent.

Estimates of patients switching or titrating medications were obtained from a retrospective analysis of pharmacy claims conducted by Verispan.[43] However, due to the time frame of that study, paroxetine CR and escitalopram were not included. Therefore, it was assumed that titration and switch rates for paroxetine CR were similar to paroxetine, and the same rates for escitalopram were based on citalopram.

■ Results

Previous studies have found that the treated prevalence of MDD is 1.9%. Taking this into account, the proportion of patients who would undergo treatment in a health plan with 500,000 individuals was estimated to be 9,500. This estimated population serves as the basis for our budget-impact model. The remission rate for first-line generic SSRIs was 35.5%, representing 3,371 enrollees with depression. Therefore, a total of 6,129 enrollees with depression would be unsuccessfully treated and moved to a second-line agent in this analysis.

Clinical Evidence

After applying inclusion and exclusion criteria, a total of 2 studies for citalopram,[44,45] 7 studies for fluoxetine,[46-52] 2 studies for escitalopram,[53,54] 4 studies for paroxetine,[55-58] 2 studies for sertraline,[59,60] and 17 studies for venlafaxine[45-61] were identified. The estimated rates of remission, response, and discontinuation rates are shown in Table 2.

Studies examining remission and response rates for treatment-resistant patients are fewer in number. For the SSRI agents, these products were included in an open-label study that examined second-line treatment of depression in a naturalistic manner compared with venlafaxine.[62] Several other studies were also available for citalopram and escitalopram,[63] fluoxetine and sertraline,[64] and venlafaxine.[65-69]

Because these studies did not necessarily report sufficient information to adjust both remission and response rates, an assumption was made that the results were consistent for both remission and response. The estimated remission and response rates for second-line treatment of depression are shown in Table 3. Relative to first-line treatment, the remission and response rates are all considerably lower than what was observed in studies evaluating treatment-naïve patients.

TABLE 4 Number of Patients Treated, Patients Achieving Remission, or Patients Achieving Response by Second-Line Agent

Product	Second-Line Market Share (%)	No. of Patients Treated	No. of Patients Achieving Remission	No. of Patients Achieving Response
Generic SSRIs	45	2,758	511	520
Escitalopram	15	919	179	181
Paroxetine CR	5	306	54	57
Sertraline	20	1,226	239	228
Venlafaxine	15	919	204	198
Total	100	6,129	1,187	1,185

SSRIs=selective serotonin reuptake inhibitors.

TABLE 5 Cost, Effectiveness, and Cost-Effectiveness of Therapies for Second-Line Treatment of Depression

Product	Total Cost ($)	Effectiveness Rate (%)	Cost per Patient Achieving Remission ($)	Incremental Cost-Effectiveness
Generic SSRIs	3,095	18.5	16,714	Referent group
Escitalopram	3,127	19.4	16,100	$3,566
Paroxetine CR	3,206	17.7	18,121	Dominated
Sertraline	3,178	19.5	16,132	$8,613
Venlafaxine	3,172	22.2	14,275	$2,073

SSRIs=selective serotonin reuptake inhibitors.

Model Outcomes

As mentioned earlier, the model projects that a cohort of 6,129 persons would fail initial therapy and move to second-line treatment. Because market share distribution for the various agents was unknown, it was assumed that all agents would have a 15% market share except for sertraline (20%) and paroxetine CR (5%). The distribution of patients and outcomes assuming this market share distribution are shown in Table 4. In this scenario, a total of 1,187 patients would achieve remission, with an additional 1,185 having a response. Comparatively speaking, as shown in Table 5, more patients receiving venlafaxine achieved remission (22.2%) than did generic SSRIs (18.5%), escitalopram (19.4%), paroxetine CR (17.7%), or sertraline (19.5%).

Data in Table 5 present results from the cost-effectiveness analysis, showing overall total costs and effectiveness for each agent and cost-effectiveness ratios. Therapy with the lowest total cost per patient was generic SSRIs with an estimated cost of $3,095. The next-lowest cost product was escitalopram with an estimated cost of $3,127, followed by venlafaxine XR ($3,172), sertraline ($3,178), and paroxetine CR ($3,206). In terms of cost per patient achieving remission, the agent with the most favorable ratio was venlafaxine XR ($14,275), followed by escitalopram ($16,100). Following the assumption that generic

SSRIs are most commonly used for second-line treatment and maintain the lowest available cost, incremental cost-effectiveness ratios (ICERs) were calculated using generic SSRI agents as the referent group (see Table 5). The lowest ICER was for venlafaxine ($2,073 per additional patient achieving remission), followed by escitalopram ($3,566) and sertraline ($8,613). Paroxetine CR dominated this analysis, meaning that it had higher cost and lower effectiveness than generic SSRIs.

Budget Impact Analysis

The AMCP *Format for Formulary Submissions* has promoted the use of both an economic model and a budget-impact analysis to accompany requests for formulary listing.[41] Consistent with these guidelines, we conducted a budget-impact analysis to determine the financial impact on a health plan by encouraging the use of cost-effective antidepressants for second-line treatment of depression. Due to a lack of data about the market share for each of the respective antidepressants used in second-line treatment, as stated earlier, the model assumed a 15% market share for most therapies (citalopram, escitalopram, fluoxetine, paroxetine generic, and venlafaxine XR), with exceptions being a 20% market share for sertraline and a 5% market share for paroxetine CR. As stated previously, an estimated 6,129 persons

in a managed care plan with 500,000 enrollees would fail first-line treatment. For this cohort, approximately 1,187 would achieve remission after switching to another agent. The estimated pharmacy cost was estimated to be $1,341,246. Total costs, including medical and pharmacy for the entire cohort, was estimated to be $19,205,737. If there was a 5% increase in the market share of venlafaxine XR, the most cost-effective therapy, and a 3% decrease in generic SSRI use as well as a 2% decrease in sertraline use, the resulting pharmacy costs would increase by $19,000, but total costs would decline by $2,000 mainly due to lower costs associated with a greater number of persons who achieved remission (1,195). Similar findings occurred if the venlafaxine XR market share was increased and other brand-name antidepressants had reductions in their market share.

Sensitivity Analysis

A series of 1-way and multiple-way sensitivity analyses were conducted to determine the impact of changing model parameters on the results. Using combined clinical data, 95% CIs were constructed for remission, response, and discontinuation rates. Using the lower bound of the 95% CI for remission and response and the upper limit for discontinuation resulted in cost per remission increasing to $16,213 for venlafaxine, $18,352 for escitalopram, $18,663 for sertraline, and $18,799 for generic SSRIs. The ICER for venlafaxine XR relative to generic SSRIs increased from $2,073 to $2,605. If the lower limits for venlafaxine XR were changed, holding constant all of the other product response and remission rates, the resulting cost per patient achieving remission increased from $14,275 to $15,176, which is still lower than the other products evaluated in the model.

■ Discussion

This study examines the cost-effectiveness of SSRIs and venlafaxine XR for second-line treatment of MDD. Results suggest that the lowest cost option was generic SSRIs, but the agent with the highest clinical success was venlafaxine XR. The ICER for venlafaxine relative to generic SSRIs was $2,072 per patient achieving remission. This result is consistent with another cost-effectiveness analysis conducted by Trivedi et al. that compared SSRI agents as a group with venlafaxine XR.[39]

The Trivedi et al. model used data from 8 double-blind clinical trials involving 2,045 patients.[39] In that study, the measure of success was a DFD, defined as having a HAM-D score of 7 or less. DFDs were then converted to QADs. The results found that persons receiving venlafaxine had a 44.9% remission rate compared with 34.7% for SSRIs. Economic analysis based on an 8-week period found that the cost for venlafaxine was $585 and for SSRIs was $526. The ICER for venlafaxine versus SSRIs was $586.08 per patient achieving remission, $14.20 per DFD, and $34.55 per QAD.

Numerous cost-effectiveness analyses have compared 2 or 3 select agents, with many involving venlafaxine.[28,30-34,70,71] These analyses do not consider the role of generic SSRIs, which are becoming more prominent with products going off patent. Those economic analyses that have included generic SSRIs assume first-line treatment of MDD.[34,37] As more generic SSRIs enter the market, it will become increasingly important to consider these market changes when conducting cost-effectiveness analyses in MDD.

Several limitations to this study should be noted. Clinical trial results were not drawn from head-to-head studies, although every clinical trial included in the study was assessed against an active comparator to minimize selection bias. Unfortunately, the published literature contains only a few studies for treatment-resistant MDD. The majority of clinical information for treatment-resistant effectiveness is derived from large open-label studies that trade greater external validity for lower internal validity. The literature is much richer concerning treatment of initial depression due to the design of clinical studies for purposes of registration and regulatory approval. More studies of treatment-resistant depression in real-world settings are needed. In addition, lack of inclusion of all potential treatments in existing studies of treatment-resistant depression limits the present study, especially with the exclusion of duloxetine. It is important to note that in this study, it was assumed that patients who failed initial therapy were transitioned into a second pharmacologic treatment. It is logical to question this assumption, but no known data could be used to estimate this transition probability.

Another limitation of this study is that the analysis did not explicitly consider differences in side effect profiles between the various agents. The results may change if substantive differences in side effect rates result in premature discontinuation or additional consumption of health care services. Another limitation is the lack of data concerning the market share for each of the respective agents as second-line therapy. We estimated a 5% increase in venlafaxine XR use for illustrative purposes in the budget-impact analysis. Actual changes in market share will vary between health plans depending on local market conditions. Another limitation is the use of WAC pricing, which may not reflect actual costs to MCOs. Finally, the analysis does not take other treatments into account, such as counseling, which may be effective for treating depressed patients.

■ Conclusion

Patients with depression often fail initial therapy, resulting in higher costs to health plans and a poorer quality of life. This analysis examines the issue of second-line treatment for depression by comparing brand-name and generically available products and taking persistency into account. Using a budget-impact and cost-effectiveness model, this study found that increasing the market share of venlafaxine XR is likely to result in overall savings to a health plan because more patients achieve

remission of their depression. This suggests that venlafaxine XR may be a cost-effective strategy with a favorable ICER for the second-line treatment of MDD.

DISCLOSURES

The author was a consultant to Wyeth Pharmaceuticals Inc. for this study. He also has served on a health economic advisory board for Wyeth related to treatment of depression. He received an honorarium for his participation in this study.

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