A Pharmacoeconomic Model for Making Value-Based Decisions About Serotonin Reuptake Inhibitors

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ABSTRACT
Managed care organizations and pharmacy benefit managers often use tiered formularies to contain drug costs. Cost is one factor used to decide tier placement. Drug prices alone may not reflect the true cost of using particular drugs within a class.

A decision-analytic model of the serotonin reuptake inhibitor (SRI) class of antidepressants was reviewed. SRIs include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). The model uses rates of adverse drug reactions (ADRs) and discontinuation rates found in the products’ prescribing information, along with other probabilities derived from the literature. The model estimates the overall direct medical costs and cost-effectiveness of SRIs in a managed care setting, taking into account the medical consequences of treatment-emergent ADRs. This paper discusses the context in which the model was constructed and its strengths and weaknesses as a tool for pharmacy and therapeutics (P&T) committees that are faced with the challenge of evaluating new and current drugs in this class.

INTRODUCTION
In terms of wholesale cost, serotonin reuptake inhibitors (SRIs) are the third largest therapeutic class of prescription drugs in the United States Criteria (IMS Health). SRIs are widely used because of their efficacy in treating depression and anxiety while being generally regarded as safe and well tolerated, especially in comparison with older classes of antidepressants, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). About 6.6% of U.S. adults (14 million people) experience major depressive disorder during a 12-month period; however, only 52% of these people receive health care treatment, and only 22% of the total number receive adequate treatment. The SRIs generated $10.9 billion in U.S. wholesale sales in 2003, trailing only cholesterol-reducing agents ($13.9 billion) and proton-pump inhibitors ($12.9 billion). Since 1994, SRIs have accounted for the majority of antidepressants used in primary care. In 2000, SRIs were prescribed during 7% of U.S. adult outpatient primary care visits.

Many SRI products are available in the U.S. today for many specific indications (Table 1). Manufacturers vie for market share within the class by highlighting clinical benefits or gaining new indications for established agents and by launching new drugs. Each event is heralded by promotional campaigns that are intended to distinguish the drugs in the minds of prescribers and consumers. As the class has grown, so has the aggregate prescribing of antidepressants. This may reflect manufacturers’ marketing activities, an increased comfort level among physicians about prescribing these agents, more favorable side-effect profiles compared with older classes of antidepressants, an increased number of indications, and heightened awareness among prescribers and consumers of the potential uses of these drugs.

Among them, the SRIs now hold nine different indications—major depressive disorder (MDD), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), social anxiety disorder (SAD), bulimia nervosa, and the newest, diabetic peripheral neuropathic pain (DPNP). No single SRI holds all nine indications; paroxetine and sertraline have the most (six).

Some SRIs have nonpsychiatric indications. Duloxetine (Cymbalta®, Eli Lilly) was recently (August 2004) allowed an indication in the U.S. for DPNP. In August 2004, duloxetine was approved for use in the European Union for treatment of stress urinary incontinence (SUI). U.S. approval of the SUI indication for duloxetine is expected early in 2005.

Clinicians may and often do prescribe SRIs without regard to their official indications. Also, some SRIs are used to treat a wide range conditions for which no member of the class currently holds an indication.

A challenge facing P&T committees, then, is to ascertain whether SRIs are clinically interchangeable. If so, managed care organizations (MCOs) can concentrate on cost in selecting drugs for formularies and assigning them to tiers. If meaningful clinical differences do exist among drugs within this large class, preferential placement in formularies of superior drugs may be warranted.

Writing in Health Affairs, the health economist J. D. Kleinke has argued:

[Hiered] prescription benefit designs will work in health plans’ long-run economic interests if and only if they are managed in a way that captures and promotes the clinical value of the best drugs, not just the financial value of the best drug deals. Drugs that do not provide a pharmacoeconomic benefit should carry the highest co-payments—perhaps even higher than the highest current tier. Conversely, a cornerstone medication for managing asthma or dia---
betes that reduces emergency room visits, and thus is found to save money in the short run, should not only carry the lowest co-payment; it should probably be fully prepaid by the health plan. It behooves the plan to carry the greatest share of the cost of those drugs it deems the most medically and economically useful.

The launch of escitalopram (Lexapro®, Forest Pharmaceuticals) in 2002 prompted the consideration of a pharmacoeconomic model of the SRI class, based on the adverse drug reaction (ADR) profiles (including discontinuation because of adverse events) of the members of this drug class. The intent of the model was to provide a useful way to view the class from a payer’s perspective, with particular focus on the impact of ADRs on the expected cost of treatment.

In the spring of 2004, the model was presented before two expert roundtables convened in San Francisco and Washington, DC, to examine clinical and pharmacoeconomic issues in the management of depression and to evaluate new tools and models to facilitate the P&T committee decision-making process. The roundtables comprised guest faculty presenters and members of the P&T community, including medical and pharmacy directors of large staff and network model MCOs and PBMs. The model was published in 2004.5

Since the creation of the model and submission of the paper reporting it, new data have become available that allow further refinement of the model. Specifically, escitalopram has gained a new indication, for GAD, and duloxetine was approved in the U.S. for use in MDD and DPNP. These events have provided additional ADR data for both drugs.

In this article, the context in which the model was developed is described, along with the rationale for the model, and its strengths and limitations. The companion article to this one (in the next issue of P&T) will present the viewpoints of participants in the roundtables about use in the P&T process of this model in particular and pharmacoeconomic models in general.

This article is presented on behalf of the P&T Society as an aid to formulary decision-makers and P&T committee members. The P&T Society is a multidisciplinary organization ded-

### Table 1: Year of FDA Approval of Indications for SRIs on the U.S. Market as of January 2005

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<thead>
<tr>
<th>Trade Name (Generic Name)</th>
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* Not included in pharmacoeconomic model. (Data from Sullivan, 2004.*)

DPNP = diabetic peripheral neuropathic pain; GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; SAD = social anxiety disorder; SRI = serotonin reuptake inhibitor; SUI = stress urinary incontinence.
aturated to enhancing formulary development and implementation across all practice settings. Its membership includes more than 3,200 physicians, pharmacists, and other professionals concerned with the P&T process.

In this article, the term SRI includes selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs).

THE AMCP FORMAT

Several nonfinancial considerations may place new drugs at a disadvantage relative to established products already on formularies. The contents of formulary kits commonly provided by manufacturers are restricted to approved promotional material. These are based on the pivotal studies conducted during the drug-approval process. When a product is new, few additional studies are available with respect to its approved indications or off-label utilization, which is extensive among CNS agents of all kinds. If an MCO makes an unsolicited request for information, however, the manufacturer is permitted to supply off-label information and unpublished articles that may be useful to P&T committees.

Since 2000, the Academy of Managed Care Pharmacy (AMCP) has urged MCOs to require manufacturers to abide by the AMCP Format for Formulary Submission. The format gives manufacturers a standardized way to submit evidence supporting a drug’s inclusion and position on a formulary. In addition to the expected material about safety and effectiveness of a drug for indicated and off-label uses, the AMCP format requests information about the drug’s role in therapy, related disease management strategies, and pharmacoeconomic data demonstrating the product’s value.

The AMCP guidelines for manufacturers may be viewed at www.fmcpnet.org/data/resource/formatv20.pdf. The specific components that manufacturers are asked to provide in their dossiers are:

- a detailed product description (20 pages, maximum)
- the product’s place in therapy (three pages, maximum)
- published and unpublished clinical study results (two pages per study)
- ancillary disease or care management strategies (three pages)
- outcomes studies and economic evaluations (two pages per study)
- an economic modeling report (20 pages, maximum)
- product value and overall cost (two pages)

The purpose of the guidelines is to enhance value, not to reduce overall drug spending. The Foundation for Managed Care Pharmacy Education educates drug company executives and pharmacists about the AMCP Format.

TRENDS IN PRESCRIPTION DRUG SPENDING

It is plausible that increased use of drugs demonstrated by solid evidence to be of high value, as opposed to only having low acquisition cost, could reduce overall health care spending over the short and long term. During the past decade, there have been large increases in drug use and spending. This is attributable to several factors (e.g., the availability of a greater number of drugs; treating more conditions; changing demographics; and increased availability of pharmacy benefits). The increased use and cost of drugs have focused attention on drug expenditures as a primary target for controlling the rapid rise in health care costs. According to the Centers for Medicare & Medicaid Services (CMS), prescription drugs accounted for 6% of U.S. health care spending in 1990, 9% in 2000, and a projected 12% in 2005.

Prescription drug spending has been the fastest-growing sector of health care expenditures for many years, increasing by 10.1% in 1998, 19.7% in 1999, and 16.4% in 2000. Since 2000, double-digit growth has continued, but at a declining pace. In 2002, the most recent year for which data are available, the growth rate had slowed to 15.3%. By comparison, in that same year, the growth rates for hospital care and physician services were 8.8 and 8.0%, respectively.

Growth in prescription drug spending is predicted to fall below 10% by 2011. CMS attributes this deceleration to slower growth in drug prices, the expiration of patent protection for some “blockbuster” drugs, and reduced demand owing to the increased use of co-payments.

The Kaiser Family Foundation attributes 42% of the overall increase in prescription drug expenditures between 1997 and 2002 to increased utilization; 34% to the replacement of older, less-expensive drugs with newer, higher-priced drugs; and 25% to manufacturers’ price increases. While the U.S. population increased by 13% between 1993 and 2003, the number of prescriptions filled rose by 70%. During that same time, the overall inflation rate averaged 2.5% per year but drug prices rose by an average of 7.4% per year.

MCOs have responded to rising drug expenses with several cost-containment strategies, including increasing the amount of the co-payment of drugs assigned to the higher tiers of tiered formularies. As of 2004, 68% of employees with employer-sponsored health insurance faced formularies consisting of at least three tiers (three tiers, 65%; four tiers, 3%).

Usually, generic drugs occupy the lowest tier, preferred drugs (branded drugs without a generic alternative) occupy the second, nonpreferred drugs the third, and other specified drugs (lifestyle or injectable drugs) occupy the fourth tier.

Between 2000 and 2004, the average co-payment for a generic drug increased by 41%, rising from $7.42 to $10.46. During the same period, the average co-payment for a preferred product increased by 62%, rising from $13 to $21, while the average copayments for nonpreferred drugs increased by 94%, from $17 to $33. The average co-payment for a fourth-tier product was $48 in 2004 (data for previous years not available).

Given that the average American fills 11 or 12 prescriptions annually, patients’ out-of-pocket expenses for co-payments can be substantial, especially when chronic conditions are involved. In a recent nationwide survey of patients ages 50 years and above, 17% of respondents reported one or more instances during the prior year when they underutilized a prescription drug because of financial concerns. Of these underutilizers, 80% reported a history of four or more chronic conditions—most frequently hypertension (67%), hypercholesterolemia (66%), depression (47%), cardiovascular disease (40%), and diabetes (30%). Of these patients, 86% used three or more
medications, including 33% who used seven or more.\textsuperscript{11}

It is well established that noncompliance with therapy for conditions such as asthma, diabetes, and schizophrenia can lead to therapeutic failure and a dramatic increase in health care use (e.g., emergency room visits, hospitalizations). Treatment failure stemming from cost-based noncompliance is treatment failure nonetheless; a question for P&T committees contemplating the addition of a new drug to the formulary is whether the drug’s tier assignment will create a disadvantage for that product, to the potential detriment of patients and the MCO if the drug brings with it greater value than other products. The question for manufacturers is how best to demonstrate such value for a drug newly arrived on the market. It is in this context that the pharmacoeconomic model of the SRI class was constructed.

THE SRI CLASS

The launch of escitalopram in 2002 spurred the interest in examining the SRI class with respect to ADR profiles and discontinuation resulting from adverse events. As a class, the SRIs appear to be no more efficacious than the older TCAs and MAOIs for the treatment of mood and anxiety disorders.\textsuperscript{12} Nevertheless, SRIs are more widely used than the older agents, partly because they have lower rates of ADRs.\textsuperscript{13}

The SRI with which a patient begins therapy often is not the agent that results in remission of the condition for which it was prescribed. Many patients fail to respond to their initial SRI, while some responders cannot tolerate the ADRs associated with that drug. Because the therapeutic goal is resolution of symptoms followed by continuation of treatment to sustain remission, such patients should be switched to another agent.

This strategy is supported by an open-label, naturalistic, nine-month trial in which depressed adults (n = 573) were randomly assigned to begin treatment with three of the other SRIs—fluoxetine (e.g., Sarafem\textsuperscript{®}, Prozac\textsuperscript{®}, Eli Lilly), paroxetine (Paxil\textsuperscript{®}, GlaxoSmithKline), or sertraline (Zoloft\textsuperscript{®}, Pfizer).\textsuperscript{14} The decision to initiate treatment was based on a primary care physician’s judgment that a patient had clinical depression warranting treatment. If a patient failed to respond adequately or could not tolerate the ADRs associated with that drug. Because the therapeutic goal is resolution of symptoms followed by continuation of treatment to sustain remission, such patients should be switched to another agent.

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In this study, 41% to 50% of patients remained on their initial SRI regimen throughout the study. The percentage of patients who remained on their initial SRI regimen for the entire nine months and scored 40 or higher on the 36-item Short Form (SF-36) Mental Component Summary (MCS) was comparable: the paroxetine group, 34%; the fluoxetine group, 37%; and the sertraline group, 37%. At the end of the study, 26% of the population met the criteria for MDD, compared with 74% at baseline and 32% at three months.

The first SRI was stopped by 20% to 24% of subjects and switched by 14% to 22%. ADRs were cited as the reason for stopping or switching by 23% to 30% of subjects, whereas 15% to 17% said they stopped or switched because of a lack of effectiveness.

Similar results were seen when the same three drugs were examined in a retrospective review of electronic medical records of patients in a Texas health plan (n = 337) who started new SRI therapy.\textsuperscript{15} Twenty-eight percent of patients had changed their medication at least once, and at least one SRI-related ADR was found in 41% of patients.

Escitalopram

Escitalopram is the S-isomer of citalopram (Celexa\textsuperscript{®}, Forest), a racemic mixture of S- and R-isomers. Isolation of the S-isomer may offer clinical advantages, as the S-isomer of citalopram has been found to be responsible for that agent’s antidepressant and anxiolytic effects,\textsuperscript{16} whereas the R-isomer lacks antidepressant or anxiolytic activity but may be associated with side effects.

Escitalopram exhibits higher selectivity for the human serotonin transporter relative to the human noradrenaline or dopamine transporters than any currently available SRI, including citalopram.\textsuperscript{17} Escitalopram is a more potent inhibitor of serotonin reuptake than citalopram. Also, escitalopram lacks affinity for postsynaptic receptors (e.g., dopamine \(D_1\) and \(D_2\), serotonin \(5-HT_{1A}\) and \(5-HT_{2A}\), adrenergic \(\alpha_1\) and \(\alpha_2\), beta, histamine \(H_1\), and muscarinic receptors). Affinity for those receptors may contribute to side effects associated with other psychotropic medications.

Escitalopram appears to have negligible effects on the cytochrome P450 enzyme system, and thus a reduced potential for drug interactions; at a dose of 20 mg, it appears to have no inhibitory effect on CYP3A4 and a modest inhibitory effect on CYP2D6.\textsuperscript{18}

Escitalopram for the Treatment of Major Depressive Disorder

The pivotal clinical trials of escitalopram that led to its approval for treatment of MDD included one fixed-dose trial, in which patients were randomized to eight weeks of treatment with escitalopram 10 mg, escitalopram 20 mg, citalopram 40 mg, or placebo; and two flexibly dosed trials in which patients were randomized to placebo, citalopram 20–40 mg, or escitalopram 10–20 mg for eight weeks. The Montgomery–Asberg Depression Rating Scale (MADRS) was the primary outcome measure in all three trials. MADRS is a 10-item scale on which each item is rated from 0 (zero) to 6, with higher scores indicating greater illness.

In a pooled analysis of the three pivotal trials, significantly greater improvement in the escitalopram group, as compared with the citalopram group, was observed at week one and week eight.\textsuperscript{19} Treatment with escitalopram 10–20 mg/day produced rapid and robust improvement in symptoms of depression, as measured by a change from baseline on the MADRS. Statistically significant differences between escitalopram and placebo were apparent from week one onward; with citalopram, statistically significant differences became apparent at week six and week eight.

Among the 715 patients who received escitalopram in these trials, the discontinuation rate owing to ADRs was 6%, compared with 2% among the 592 patients receiving placebo. In the
fixed-dose studies, however, the discontinuation rate owing to ADRs for patients receiving escitalopram 10 mg (the recommended dose for initial treatment of MDD) was not significantly different from that of patients receiving placebo.20 Among the patients receiving escitalopram 20 mg, the ADR-associated discontinuation rate was 10%, which was significantly different from the discontinuation rates in the escitalopram 10 mg (4%) and placebo (3%) groups. In patients with moderate to severe depression (n = 195), escitalopram 20 mg has been shown to be as effective as extended-release venlafaxine (Effexor® XR, Wyeth-Ayerst) 225 mg in improving depressive symptoms and in achieving remission.21 After eight weeks, remission was reported in 41% and 37% of escitalopram and venlafaxine XR patients, respectively. Nevertheless, the incidence of treatment-emergent ADRs was higher in the venlafaxine XR group than in the escitalopram group (85% vs. 68%), as was the discontinuation rate. Sixteen percent of patients receiving venlafaxine XR dropped out of the study, compared with 4% of the escitalopram patients.

Escitalopram 10 mg has been compared with optimally dosed sertraline—50 to 200 mg—in patients with MDD.22 Both treatments were well tolerated, with ADR-related discontinuations seen in only 2% and 4% of the escitalopram and sertraline groups, respectively, and 85% and 86% of the escitalopram and sertraline groups completing the eight-week trial. By the end of the trial, the median sertraline dose was 150 mg, and 45% of patients in the sertraline group were receiving the 200-mg dose. Both treatments were equally effective in achieving clinically meaningful improvements in MADRS scores. Likewise, both treatments were equally effective in improving symptoms of anxiety, which are seen in up to 90% of patients with depression.23

Escitalopram for the Treatment of Generalized Anxiety Disorder
In December 2003, escitalopram received FDA approval for its second indication, the treatment of GAD. The indication was based on three eight-week placebo-controlled studies. In all three studies, patients receiving escitalopram 10–20 mg showed significantly greater improvement in the Hamilton Anxiety Scale (HAM-A) than did patients receiving placebo.

For long-term (24-week) treatment of GAD, escitalopram 10–20 mg has been shown to be as effective as paroxetine 20–50 mg.24 All-cause discontinuation rates were 47% and 36% in the paroxetine and escitalopram groups, respectively, with discontinuation because of ADRs reported in 23% and 7% of the paroxetine and escitalopram groups, respectively. Over the course of the study, an increase in body weight of 7% or more was observed in 18% of the paroxetine group vs. 8% of the escitalopram group.

Duloxetine
Duloxetine came onto the U.S. market after the pharmacoeconomic model was completed. It is briefly described here because it would have to be incorporated in updates to the model.

In contrast to escitalopram, which selectively inhibits serotonin reuptake, duloxetine inhibits reuptake of both serotonin and norepinephrine (as do venlafaxine and venlafaxine XR).

Yet, as was seen in the study by Bielski (2004)21 comparing venlafaxine XR and escitalopram, the dual inhibition provided by venlafaxine XR did not provide any efficacy advantage over the single inhibition afforded by escitalopram. Likewise, duloxetine 40–120 mg was not statistically significantly superior to fluoxetine 20 mg in the treatment of patients with MDD.25 Duloxetine 80 mg was superior to paroxetine 20 mg in the treatment of MDD, however.26

In the placebo-controlled trials of duloxetine for the treatment of MDD, the ADR-related discontinuation rates for duloxetine and placebo were 10% and 4%; for treatment of DPNP, the respective discontinuation rates were 14% and 7%.27 In both the MDD and DPNP trials of duloxetine, patients who were randomly assigned to receive duloxetine lost a mean of 0.5 kg and 1.1 kg, respectively, whereas patients receiving placebo gained a mean of 0.2 kg in the trials for either indication.

THE PHARMACOECONOMIC MODEL
Interest in developing a pharmacoeconomic model of the SRI class was stimulated by the launch of escitalopram in 2002. All members of the SRI class have been generally regarded by prescribers and MCOs as being efficacious, and hence distinguishable, from the perspective of a health plan, primarily on the basis of acquisition cost. It seemed desirable to build a model that could examine whether the varying ADR profiles among members of the class might further distinguish the SRIs on the basis of their effect on the direct health care costs incurred by a health plan among its members using SRIs, over and above the acquisition price of these products.

It was believed that such a model might be a welcome addition to the previously described AMCP Format and would prove useful to P&T committees considering adding a new SRI to the formulary at a time when information about the new product is necessarily lacking. The original intent was to build a model using ADR rates from published head-to-head studies of the SRIs, but a literature search showed a dearth of published articles adequate for that purpose. In lieu of published head-to-head comparisons, prescribing information for the various SRIs was used instead as a source of information about ADR rates for each agent compared with a common denominator (placebo).

The pharmacoeconomic model included the eight SRIs that were available in the U.S. in mid-2003 for the treatment of MDD: citalopram, escitalopram, fluoxetine, paroxetine, controlled-release (CR) paroxetine, sertraline, venlafaxine, and venlafaxine XR. The model has been described in detail elsewhere.5 Simply put, the placebo-corrected incidence of ADRs for each agent served as the basis for computing the direct costs of medical treatment for each agent and its relative effectiveness.

The key assumptions behind the model are as follows:

- The duration of the treatment period was six months.
- The goal of treatment was to achieve a therapeutic response, defined as greater than a 50% reduction in the baseline MADRS score by week eight and the completion of a 180-day course of therapy.
- The efficacy of all agents was assumed to be equal: the response rate was set at 60% for all agents.

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- Medical costs encompassed drug costs, physician visits, the direct cost of therapeutic failure, the direct costs of treating ADRs, and the costs of dose titration or switching to another agent because of ADRs.
  - Drug costs were based on prices listed at a U.S.-based online pharmacy, www.drugstore.com, and discounted by an additional 10% to reflect the average rebate-reduced acquisition costs available to MCOs and PBMs.
  - The cost of a medical visit was set at $63, the 2003 Medicare reimbursement rate.
  - All patients had one baseline visit.
  - All ADRs required one additional visit, with the exception of headache, excitation, or sexual ADRs, which required two additional visits.
  - Most ADRs (95%) were treated nonpharmacologically or with an over-the-counter product instead of a prescription drug (5%).
  - The cost of treatment failure was set at $8,141 (range, $5,520 to $10,309). The base-case cost of treatment failure was estimated from the low end of the range of recently published estimates from a managed care setting, and the range was derived from the low and high end of estimates in the literature. These estimates include the direct medical costs of physician visits, switches, and augmentations, as well as potential hospitalizations and suicide attempts.
  - In lieu of head-to-head clinical trials comparing the incidence of ADRs across the SRI class, ADR and discontinuation rates were based on information in the products’ prescribing information across all indications.
  - The probabilities of various events associated with SRI treatment were based on the previously mentioned study of electronic medical records in a Texas health plan.
    - developing an SRI–treatment-emergent ADR requiring a physician visit: 41%
    - discontinuation: 19%
    - switching: 22%
    - adding drug therapy to treat the ADR: 23%
    - dosage adjustment: 6%
    - no change: 30%
  - Patients who were switched two times or more were deemed treatment-resistant.

Based on these assumptions, the model showed there was a 67% chance that treatment with escitalopram would result in the lowest expected cost, $3,891, followed by citalopram, $3,938 (25% chance), and fluoxetine (generic), $4,034 (8% chance). Sensitivity analyses revealed that these results were consistent regardless of any reduction in the acquisition price of generic fluoxetine or generic paroxetine.

STRENGTHS AND LIMITATIONS OF THE MODEL

The strengths and limitations of the current model must be understood within the context of what questions a pharmacoeconomic model can and cannot answer for P&T committees. Pharmacoeconomic models are not meant to predict with certainty the outcome of treatment. Instead, models should be used to provide important insights into the implications of factors about which incomplete information is available (such as the relative incidence of ADRs among SRIs) and their impact on the expected cost and effectiveness of treatment. The information from such a model can help P&T committees determine if these factors are significant and relevant to the desired treatment outcomes.

One of the current model’s strengths is that it presents a standardized method for comparing members of a therapeutic class when head-to-head clinical trials are lacking. An obvious limitation of the model is that it necessarily was constructed in the absence of direct head-to-head studies with cost/pharmacoeconomic outcomes measured prospectively. The model relies on comparisons to a common denominator (placebo) to derive the relative ADR profiles of marketed SRIs. The product information-based ADR rates are transparent, however, and these assumptions can be changed by a P&T committee to include more specific information about the relative incidence of ADRs in their population.

When used in this manner, the model could be useful to health plans desiring to assess the overall expected cost of treatment with different SRIs specific to their population. Yet even in the absence of providing plan-specific ADR rates, the general model provides some important and relevant information that can be useful to P&T committees:

1. It appears that the incidence of ADRs across SRIs has a significant impact on the total cost and effectiveness of treatment. After a variety of sensitivity analyses, the results of the original model consistently showed that the SRI with the lowest ADR incidence rates resulted in the lowest expected cost of treatment and the greatest effectiveness. Hence, if the P&T committee has strong evidence to believe that one SRI has been proven to have a better tolerability profile in its health plan, it is likely that use of this SRI will result in the lowest expected cost of treatment and greatest effectiveness.

2. Treatment failure is the biggest cost driver and ADRs can be a significant factor in rates of treatment continuation. Health plans should consider formulary policies that encourage physicians and patients to find the treatment that will be most successful in promoting remission. The model’s results suggest that the SRI with the lowest ADR rate will likely have the lowest treatment failure rate.

There are limitations to the model. First, much of the information in the package inserts (PIs) for SRIs has changed since the original analysis. For example, escitalopram has gained a second indication for GAD and is expected to receive indications for panic disorder and SAD this year; duloxetine has received indications for MDD and DPNP and is expected to receive an indication for SUI this year. (See next paragraph on page 105 for more about the introduction of duloxetine.) These types of changes need to be incorporated to determine the relative incidence of ADRs based on the most recent data available. In the original model, treatment with escitalopram resulted in the lowest expected direct cost, largely because of the fact that it had the lowest ADR rates of all SRIs. The model consistently showed that the SRI with the lowest ADR inci-
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dence resulted in the lowest treatment cost. If the incorporation of the new PI data (or any other data) suggested that a different SRI had the lowest ADR incidence, the results of the model would most likely favor that drug.

Second, a new SRI, duloxetine, has joined the class since the model was created. In some respects, it appears to have a slightly less favorable ADR profile than escitalopram and it is more expensive. It is unclear how duloxetine would compare to other SRIs, but it is unlikely that treatment with duloxetine would result in the lowest expected cost of treatment unless its ADR profile were superior. Also, patterns of care for the treatment of ADRs may have changed. For example, as a result of its withdrawal from the market, rofecoxib (Vioxx®, Merck) would not be used to treat headache, as assumed for a small percentage of those experiencing it in the model. However, sensitivity analyses of the original model showed that these factors did not affect the model results and it is unlikely that even significant changes in the drug cost of treating ADRs would change the model results.

A third limitation is the reliance on ADR rates from the prescribing information. In the absence of head-to-head comparative trials of all SRIs, the model was based on comparative data available in the PI and compared all SRIs to the common alternative of placebo. The model notes the cautionary language in the prescribing information of many SRIs. For example, the Effexor® PI states the following:31

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators.

This limitation is acknowledged, but an alternative source of information is not available. As stated previously, if health plans believe that one SRI has a better ADR profile, it is likely that treatment with that SRI would result in the lowest cost and greatest effectiveness.

CONCLUSION

In summary, the model suggests that ADRs associated with individual SRIs may significantly affect the overall cost of treatment. The model shows that the SRI with the lowest incidence of ADRs is most likely to result in the lowest expected cost of treatment and the greatest effectiveness. The preliminary results derived from the model suggest that use of escitalopram may result in lower overall costs relative to other SRIs as a result of its lower incidence of ADRs.

In sum, pharmacoeconomic models can provide insight into the impact of a variety of factors that may affect the total cost of treatment. Models can distinguish drug acquisition price and other determinants of the total cost of treatment. In particular, the model shows that the biggest driver of treatment cost for depression is not the drug acquisition price but rather the incidence of ADRs. Also, the model highlights the fact that ADRs can be a significant deterrent to treatment continuation. The implication for P&T committees is that health plans should consider formulary policies that encourage physicians and patients to use treatments that will successfully promote remission, because the costs of treatment failure dwarf the relative differences in drug acquisition price.

The March 2005 issue of P&T will feature a discussion of this model by a roundtable of your colleagues.

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Pharmacoeconomic Model for SRIs

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