Managed Care’s Response to a Pharmacoeconomic Model of Serotonin Reuptake Inhibitors

Patrick W. Sullivan, PhD, Robert Valuck, PhD, RPh, Diana I. Brixner, PhD, and Edward P. Armstrong, PharmD

This article summarizes the responses provided by participants in two roundtable discussions to a pharmacoeconomic model of the class of serotonin reuptake inhibitors (SRIs).*

A decision-analytic model was developed to examine the potential impact of differences in adverse drug reactions (ADRs) reported in the prescribing information of eight currently marketed SRIs on the expected cost of treatment and to provide preliminary data that may assist P&T committees in making decisions about this class (Table 1). The discussants (Table 2) included representatives of managed care organizations (MCOs) and pharmacy benefit managers with extensive experience in the P&T decision-making process.

Sponsored by Forest Pharmaceuticals, the roundtables were held on March 31, 2004 in San Francisco and in Washington, DC, in conjunction with the P&T Society’s annual meeting on April 21, 2004. Since then, the model discussed at the meetings has been published.† The model was refined, and its application by P&T committees was discussed in the February 2005 issue of P&T.‡

AMCP FORMAT

The Sullivan model is intended to be used together with a comprehensive dossier submitted by pharmaceutical companies to health plans using the format devised by the Foundation of the Academy of Managed Care Pharmacy (AMCP). The participants said many pharmaceutical companies submit dossiers to P&T committees, but few scrupulously follow the AMCP format. One MCO official reported devising a check-

* In this article, the term serotonin reuptake inhibitors (SRIs) is employed to encompass both the selective serotonin reuptake inhibitors (SSRIs) and the serotonin and norepinephrine reuptake inhibitors (SNRIs).

† In the earlier P&T article on this model (February 2005), the following text appeared:

“One 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.”

In the interim, the duloxetine application for stress urinary incontinence (SUI) was withdrawn from the U.S. Food and Drug Administration review based on the data package that was submitted. This does not, however, affect the duloxetine indication for depression and for diabetic peripheral neuropathic pain in the U.S. or SUI and depression indications outside the U.S.

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or reject them. That committee, despite observations by the pharmacy director that the products will adversely affect the pharmacy budget, routinely has accepted clinically superior drugs. Another individual represented a health plan P&T committee that gives equal consideration to financial and clinical problems. One participant noted that a fixed-dollar cap on subscribers’ pharmacy benefits often affects patient willingness to accept prescriptions for any “third-tier” drugs that count toward those limits.

One participant remarked that if pharmaceutical companies desire to command the attention of a P&T committee, information should be presented about absolute risk reduction (ARR) and the corresponding number needed to treat (NNT) associated with use of a drug. This attendee’s main point was that relative risk reduction information can sometimes be misleading or can overstate the apparent importance of a finding when the ARR is small. For example, cutting the incidence of a side effect or adverse clinical outcome during a course of treatment in half (relative reduction of 50%) sounds impressive, but if the 50% reduction is a reduction of an absolute rate of 1.0% down to 0.5%, the relative risk might be misleading as the absolute advantage is small. The corresponding NNT is equal to 1/ARR. In this case, 200 patients would have to be treated to prevent one bad outcome. Inclusion of the NNT often is very useful in making P&T decisions.

Participants also pointed out that presentations should emphasize clinically significant differences of a treatment or among treatments, not merely statistical significance. P&T decisions are based, first, on clinical significance and only secondarily on economic considerations. In that context, the Sullivan (2004) model of differences in the incidence, type, and costs of adverse drug reactions (ADRs) associated with the use of different SRIs may be clinically significant to patients and may provide potentially useful information on the financial effects of these differences. Head-to-head clinical trials have not been done to determine clinically or statistically significant differences in ADR incidence and cost among agents, thus necessitating that these projections be based on the package insert data. Therefore, sensitivity analysis, when it allowed the parameters to be varied, was deemed extremely helpful by the authors.

**INCLUSION OF GENERIC PRODUCTS**

The effect of ADRs on overall treatment costs among SRIs can be substantial. In the model presented during the roundtables, a branded SRI, escitalopram (Lexapro®, Forest) incurred the lowest overall expected cost over the course of six months, ahead of another branded SRI, citalopram (Celexa®, Forest), and a generic SRI, fluoxetine. (Table 1 presents a list of drugs included in the model.) Even if the cost of generic fluoxetine or generic paroxetine were reduced to $0, the model still showed escitalopram therapy to be the most cost-effective strategy, because it had the lowest rate of ADRs within the class.

The promotion within a benefit plan of a branded product over generic drugs can be difficult. Several participants said that even if a model shows that the overall cost of any branded product is lower than that for any other product, including generics, that drug could be grouped with the generics; the generics, however, would not be placed at a disadvantage if the branded drug received a more favorable position on the formulary. Once physicians have adopted the habit of prescribing generics, the participants said, it is undesirable to attempt to induce them to abandon that habit by structuring a formulary so as to favor a branded product over generic ones.

The participants said that since the time generic SRIs became available, one way in which their utilization has been encouraged is by requiring physicians to obtain prior authorization for continued use of branded products. The use of generic SRIs also has been driven by cost-containment strategies that cap the annual amount of drug reimbursement. Under this system, physicians may prescribe as they see fit, but patients—instead of demanding a branded drug that necessitated prior authorization per the rules of the formulary—now worry about exceeding their cap. As a result, patients may resist the prescription of a branded product instead of a generic one. A drug on a higher tier of such a formulary might not be prescribed with any regularity, because its co-payment may be too high relative to a drug benefit cap or because it exhausts the benefit limit for a patient using multiple drugs.

Participants said that the Sullivan model might be useful for helping P&T committees decide on the tier to which an SRI is assigned. As matters stand, generics will be favored as first-line therapy.

**USEFULNESS OF THE MODEL**

Participants said that, from the perspective of a health plan, the problem with many pharmacoeconomic models is that they deal with costs occurring outside the health plan, such as quality of life and absenteeism. These concerns may be important to employers, but a health plan is interested in events that have an impact on the overall budget of the health plan (e.g., rates and costs of hospitalizations and office and emergency room visits). This approach may differ for health plans in which the major client base consists of employers.

The participants said that the only kind of pharmacoeconomic model that a P&T committee should trust is one that is transparent (i.e., where all assumptions, rates, and costs are

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**Table 1 | SRIs Included in the Sullivan Model**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
</tr>
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<tbody>
<tr>
<td>Citalopram</td>
<td>Celexa®</td>
<td>Forest</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro®</td>
<td>Forest</td>
</tr>
<tr>
<td>Fluoxetine*</td>
<td>Prozac®, Sarafem®</td>
<td>Lilly</td>
</tr>
<tr>
<td>Paroxetine*</td>
<td>Paxil®</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Paroxetine controlled release</td>
<td>Paxil® CR</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor®</td>
<td>Wyeth-Ayerst</td>
</tr>
<tr>
<td>Venlafaxine extended release</td>
<td>Effexor® XR</td>
<td>Wyeth-Ayerst</td>
</tr>
</tbody>
</table>

* The generic product was used in the model.
Table 2  Roundtable Discussants

<table>
<thead>
<tr>
<th>MODERATORS</th>
<th>PARTICIPANTS</th>
</tr>
</thead>
</table>
| **Joseph Eichenholz** *  
Executive Director, Pharmacy & Therapeutics Society  
Glastonbury, Connecticut | **Jeffrey Casberg, MS, RPh §**  
Director of Pharmacy  
ConnectiCare, Inc.  
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Regional Clinical Director  
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| **Jerry Miller, PharmD §**  
Senior Consultant  
Health Strategies Group  
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Chief Medical Officer  
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Clinical Pharmacist  
InterHospital Physicians Association  
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and Science  
Investigator, Center for Health Outcomes and Pharmacoeconomic Research  
University of Arizona College of Pharmacy  
Tucson, Arizona | **Eugene R. Eavy, RPh, MBA **§  
Director, Pharmacy Services  
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Executive Director, Pharmacotherapy Outcomes Research Center  
University of Utah Health Sciences Center Salt Lake City, Utah | **Angeli Garg, PharmD, MBA §**  
Clinical Pharmacist  
Santa Clara Family Health Plan  
Santa Clara, California | **Ira L. Salom, MD** *  
Geriatrics, Clinical Pharmacology  
HIP/Mount Sinai School of Medicine  
Elmhurst, New York |
| **Perry Cohen, PharmD, FAMCP** *  
Principal, The Pharmacy Group LLC  
Glastonbury, Connecticut | **Robert Gilkin, Jr., RPh, MBA §**  
Regional Pharmacy Director  
Coventry Health Care  
Williamstown, New Jersey | **David M. Yoder, PharmD, MBA** *  
Vice President, Pharmacy Services  
Mid Atlantic Medical Services, Inc.  
Columbia, Maryland |
| **Robert Valuck, PhD, RPh §**  
Associate Professor of Clinical Pharmacy  
Director, Program in Pharmaceutical Outcomes Research  
University of Colorado School of Pharmacy  
Denver, Colorado | **Humberto Guerra-Garcia, MD, MPH** *  
Senior Medical Director  
Quality and Risk Management  
Keystone/AmeriHealth Mercy Health Plan  
Philadelphia, Pennsylvania | |
| **Paul Kociemba, RPh, MS §**  
Senior Manager of Pharmacy  
Priority Health  
Grand Rapids, Michigan | **Note:** Affiliations of the participants reflect those during the roundtable discussions in April 2004. |

* Attended the roundtable held on April 21, 2004, in Washington, DC.  
§ Attended the roundtable held on March 31, 2004, in San Francisco, California.
Response to a Pharmacoeconomic Model of SRIs

shown to readers and, ideally, can be altered by readers to fit their own circumstances) and one that a committee could adapt to suit the demographic characteristics of its own plan. It is extremely important to know the assumptions behind the sensitivity analyses in a model, they said, because those assumptions may not correspond with the experience of a given health plan. In addition, a good model must be able to evaluate all products in a class and must be flexible enough to accommodate market changes.

The ability to customize the model depends on the availability of specific health plan data. In one organization, there would be access to pharmaceutical data, but the medical data might be less complete or less detailed. Merging pharmacy and medical data can be extremely difficult.

**CREDIBILITY OF THE MODEL**

The Sullivan model appears credible, the participants said, in that the mathematical equations did not seem to have been forced into the service of a desired result. Participants felt that this model seems to have been built on conservative, common-sense assumptions that are easily understood. When the user of a model understands that the model is driven by realistic assumptions, the model begins to make sense conceptually instead of seeming to be just a “numbers game.”

Some participants indicated that they had previously seen similar decision trees that were constructed for cyclo-oxygenase-2 (COX-2) inhibitors, osteoporosis drugs, and antidepressants. The depression model incorporated rates of partial effectiveness, which led to additional visits for titration of the original agent or the addition of a second agent—followed by reduced rates of compliance owing to poly-pharmacy. Such a model is complicated, but it does take into account real-life issues.

One participant stated that the high rate of side effects leading to a medical intervention in the Sullivan model is surprising, because the only SRI-related side effects that seem to concern physicians are sexual ADRs. Patients complain about sexual dysfunction, but not about gastrointestinal side effects.

A pharmacy consultant questioned the model’s reliance on varying ADR rates. Considerable patient variability is seen among these drugs, that participant said, and it is difficult to quantify the effect of ADRs. For example, diarrhea might develop, but it usually resolves within a week. Although diarrhea is an ADR, the panel wondered whether it is an ADR that leads to further spending by the health plan. In the real world, ADRs are not the only reason people switch or stop using an SRI. In its current form, the model is a “great academic exercise,” a participant said, but it would be surprising to see the model hold up when health plan data are incorporated.

One difficulty in constructing a model on the basis of the incidence of ADRs reported in the prescribing information is that such an approach captures only the ADRs that occurred during the clinical trial phase. Broader ADR rates need to be measured, because once a drug is on the market, different ADR rates are observed. After a drug has been marketed, it is also likely that rare but costly ADRs will emerge, and their cost will eclipse that of the simple ADRs seen during the clinical trial phase of drug development.

A participant pointed out that instead of relying on ADR data from U.S. prescribing information, such data could be acquired from European countries, where the reporting of ADRs is required by regulatory bodies, in contrast to the voluntary reporting of ADRs in the U.S. The model’s authors considered European ADR data as a possible source of information, but the main problem with this approach is that the populations and treatment patterns can vary greatly from country to country. The regulatory environments, reporting methods, and incentives also can differ greatly, and ultimately, decision-makers in the U.S. rarely seem to want to rely on European economic data to make decisions in their populations. Therefore, U.S. data were used when available.

A participant suggested that although the cost of ADRs might be quantifiable in a large population, it is difficult for a smaller health plan to examine its data and to attribute an adverse event to a drug. Another participant, however, explained that the Sullivan model was based on a study that did just that—it examined the electronic medical records from a Texas health plan to find the association between SRI-related ADRs and physician visits.

**“SILOS”**

Regardless of how credible and useful a pharmacoeconomic model may seem, the reality is that in many health plans, the pharmaceutical costs still are widely “siloed”; that is, they are considered separately from medical costs. A participant pointed out that if pharmacy managers are under pressure to work within a given pharmacy budget, the potential of a drug to affect costs outside the pharmacy silo will receive only minimal consideration. Thus, the nature of an organization’s business model is a factor in determining whether a pharmacoeconomic model such as the Sullivan model would be of interest to a P&T committee.

In a system where claims for outpatient and inpatient visits are carved out separately, this particular model would not work, the participants said. It might have some potential for justifying pharmacy expenses, but contracts that are negotiated in silos do not allow for the overall lowering of expenditures.

**CONCLUSION**

The Sullivan pharmacoeconomic model of the SRI class was generally well received by managed care officials with experience in the P&T decision-making process. The extent to which the model might be used by a P&T committee depends, first, on whether the committee gives consideration to pharmacoeconomic arguments. If so, the potential utility of the model next depends on whether the model can be customized to reflect the organization’s demographic and utilization profiles, and whether it can be updated to reflect changes in the marketplace.

**REFERENCES**


The P&T Society, a nonprofit professional association serving the needs of the P&T community, is dedicated to promoting the review, discussion, and dissemination of the evidence used to generate drug utilization decisions by major health care systems, both public and private. P&T community members (hospitals, employers, health systems, government agencies, managed care organizations, long-term care, and correctional health care) seek information that demonstrates the effectiveness and value of products when discharging their responsibilities of adding and/or removing medications from an organization’s list of approved drugs. They face growing pressure to contain drug costs and maintain quality of care, greatly increasing the complexity of the formulary decision and management process. As part of its mission, the P&T Society routinely examines the processes and procedures used by health care delivery systems in the interest of ensuring the delivery of high-quality, outcomes-oriented health management in an array of settings.

P&T is the Society’s official publication. More information about the Society may be obtained at www.PandTSociety.org.

Disclosure

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