The Use of Pharmacoeconomics in Formulary Development: Can This Improve the Way Deep Vein Thrombosis Is Treated?

Based on a presentation by T. Jeffrey White, PharmD, MS

Presentation Summary

A study of the Prescription Solutions database revealed that in 2000 the average pharmacy plus medical costs per patient with deep vein thrombosis (DVT) were $60,019. The total charges for this group of patients in this organization were $389 million. The cost of treating these patients is relatively high, and there may be opportunities to significantly improve the quality and overall cost effectiveness of their care. One example of how this might be accomplished is by developing a pharmacy-based DVT predictive model that could be used proactively to identify patients who may be at risk for DVT and who might benefit from early intervention with low-molecular-weight heparin therapy prophylaxis.

Prescription Solutions, a pharmaceutical benefit manager, is a wholly owned subsidiary of PacifiCare Health Systems. Prescription Solutions is a fully integrated pharmacy and medical management company that provides services to approximately 5.5 million people. The company currently has more than 600 employees located in Costa Mesa and Carlsbad, California. Prescription Solutions manages the pharmacy benefit for the largest Medicare risk plan, Secure Horizons.

Prescription Solutions processes pharmacy claims, maintains a formulary, develops and implements pharmacy-based disease-state management programs, and conducts health-outcomes research. They have access to a pharmacy and medical database with information on approximately 4 million people, covering more than 4 years. The database includes pharmacy data on more than 5.5 million people and medical data on more than 4 million people. One million of those are older people covered by Medicare, and the remaining approximately 3 million people are covered by commercial insurance. Approximately 10% of the lives for which medical data are available are covered by commercial insurance. Each year, there is approximately a 20% turnover in Secure Horizons' membership. Laboratory data are available for approximately 500,000 people. The database has information ranging from incidence of recurrent events, number of hospitalizations, and frequency of emergency department visits to patient compliance, laboratory, and potentially, quality-of-life data. The role of the research team is to measure pharmacy use patterns (ie, compliance, dosage titration, medication switching, concurrent use) and medical use patterns (ie, frequency of thromboembolic events, emergency department visits, hospitalizations, physician visits, clinical end points, and total cost of therapy). Pharmacy and medical use patterns can be integrated to estimate the potential influence of pharmacy use patterns on total healthcare outcomes (ie, cost, utilization, clinical outcomes, and quality of life). These data can be very useful for formulary decision making.

The use of such a database in retrospective studies can provide valuable

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information regarding the effectiveness of particular pharmaceuticals—that is, their ability to perform effectively in a real-life environment. In contrast to efficacy studies, which are typically prospective, randomized, controlled trials that are performed in a "pristine" environment, effectiveness trials are prospective or retrospective, occur after the drug's launch, and are naturalistic studies that measure clinical, economic, and humanistic outcomes. Effectiveness studies, which measure the performance of a drug in a real-world environment, complement efficacy studies, which examine a drug's ability to reach predetermined clinical markers such as preventing deep vein thrombosis (DVT).

Prescription Solutions also performs predictive modeling analyses. This involves analyzing pharmacy data from the company's database and using it to predict future total healthcare expenditures or future catastrophic events such as DVT or pulmonary embolism. The resultant model can be used to predict which patients are likely to have a catastrophic event. Such patient-prediction information can be used by medical groups to determine capitation settings or by employers to determine the disease-severity level of a particular population for underwriting purposes.

Another service that Prescription Solutions provides is pharmacoeconomic modeling. This involves the examination of generalized patient outcomes or of a client's specific outcomes, stratified by age, sex, and region, to determine that group's disease-severity level. The company also provides decision analyses, multiattribute utility analyses, and epidemiologic and burden-of-disease analyses, which use actual clinical data.

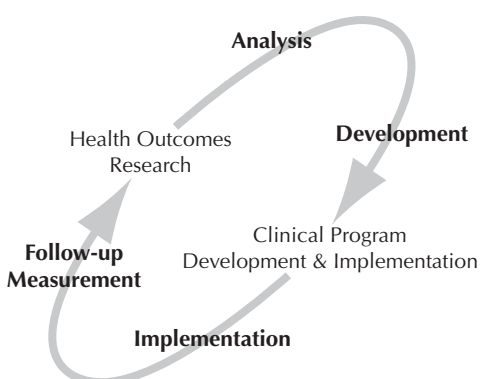
These forms of health-outcomes analyses can be used to develop and manage evidence-based programs. Thus, these analyses are used to support the pharmacy and therapeutics decisions of both the firm and its clients. The combination of results from prospective, randomized, controlled trials and results from effectiveness analyses of retrospective database information can produce compelling evidence for or against the usefulness of a particular drug.

The analyses can also be used to develop and implement prior authorization guidelines. Such guidelines are created to ensure that the appropriate drug is administered to the appropriate patient under the appropriate circumstances, and that inefficiency from underuse or overuse of particular pharmaceuticals is avoided.

The company also provides clinical program support, including disease-state management, quality improvement and utilization management, and forecasting through predictive modeling. Drugs are selected for formulary use according to the following criteria: safety, efficacy, cost and cost effectiveness, patient acceptance and ease of use, medical and pharmacy cost offsets, number of indications, and track record. Safety is the most important criterion, because an unsafe drug is harmful both to the public and to the reputation of the pharmaceutical industry. Cost effectiveness is also an important criterion. The most expensive drug may actually be the most cost effective. For example, if one form of low-molecular-weight heparin (LMWH) is expensive but prevents a significant proportion of events related to DVT and pulmonary embolism, it may actually be less costly per event prevented than other products.

The overall goal of clinical program support is to manage a particular patient population more effectively by performing

Figure 1. Clinical Program Cycle



health-outcomes research to find opportunities for intervention and modification of patient behavior. This dynamic process is shown in **Figure 1**. It involves careful and repeated measurement of the clinical, economic, and humanistic (including quality of life, patient satisfaction, and productivity at work and school) outcomes from a particular clinical program. In this process, the perspectives of all stakeholders are considered, including the physician, the patient, the health management organization, the pharmaceutical company, the employer, and overall society. For example, if patient compliance is not optimal, the firm can develop an educational intervention program that is based on health-outcomes research and can be used by physicians, patients, and providers. Once the program has been developed and implemented, the firm can measure its impact and change or enhance the program to ensure that patient compliance is improved.

Use of the Database

Information in the company's database was used to analyze whether completion of antidepressant treatment is associated with lower total healthcare costs than noncompletion of treatment.[1] This type of analysis can be performed for any kind of medication, including LMWH. Data from the records of 4980 patients were examined, including information about the patient's first diagnosis and the beginning of antidepressant therapy. Data for the 6-month period following the initiation of treatment were examined for patient compliance with therapy, and data for the full year following the initiation of therapy were examined to determine the patient's total healthcare costs.

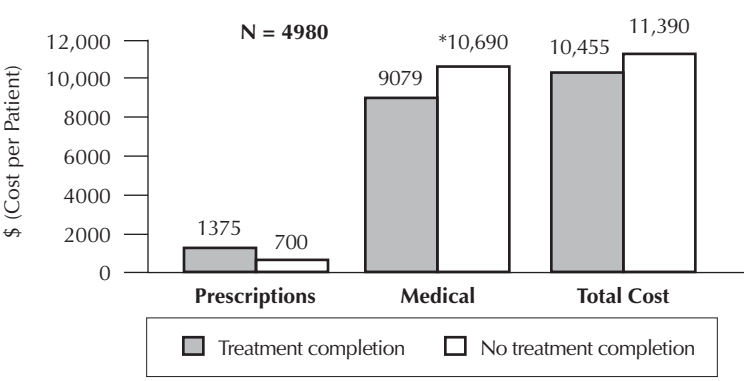
The analysis showed that, over 1 year, the average pharmaceutical costs per patient were $973, and the average medical costs were $10,036, for a total average cost per patient of $11,009. The costs per patient were also examined by dividing patients into those who completed antidepressant therapy and those who did not. These data are shown in **Figure 2**. For patients who completed therapy, the cost for medication over the year was $1375; medication costs for those who did not complete therapy were $700 for the year. However, medical costs were significantly lower for those who completed therapy ($9079) compared with those who did not complete antidepressant therapy ($10,690) ($P$ <.001). The total average cost per patient was $10,455 for those who completed antidepressant therapy and $11,390 for those who did not.

The firm also carries out compliance studies comparing the use of once-daily dosing with twice-daily or more frequent dosing. One such study by Prescription Solutions compared a glaucoma medication given once a day with medications that were administered twice a day and 3 times a day. A proportional hazard regression analysis showed that the once-daily and twice-daily drugs were significantly more likely to be taken by patients than the medication that required dosing 3 times a day.

Prevalence and Prevention of DVT

According to the company's data, during 1999, approximately 6477 patients (or 2.87 cases per 1000 patients) in the database received an *International Classification of Diseases, 9th revision* diagnosis code of 453, or venous thrombosis. Of these patients, 59% were women; their average age was 69

Figure 2. Antidepressant Treatment Completion Study



*P <.001.

This type of analysis can be done for any kind of medication, including low-molecular-weight heparins.

Figure 3. Sample Scoring Tool

Instructions: COX-2 inhibitors will be approved for use if condition 1 is met:

Patient is at high-risk level for gastrointestinal (GI) complications of NSAID treatment as determined by the scoring tool below. Write the appropriate points in the right-hand column. After answering all the questions, add up the points and see the bottom guidelines.

			Points
1. Patient diagnosis			
OA or RA	6.4 points	No OA or RA 0 points	☐
2. Patient age			☐
Age 20 or younger	0 points		
Age 21-30	5.8 points		
Age 31-40	7.7 points		
Age 41-50	9.7 points		
Age 51-60	11.6 points		
Age 61-70	13.6 points		
Age 71-80	15.5 points		
Older than age 81	17.4 points		
3. Has the patient ever been hospitalized for GI problems such as bleeding *or* an ulcer?			☐
No	0 points		
Yes	18 points		
4. Is the patient currently taking steroids?			☐
No	0 points		
Yes	3.7 points		
5. Is the patient currently taking warfarin?			☐
No	0 points		
Yes	6.9 points		
Sum of scores:			☐

Risk of GI complications = exponent ((sum of scores/10) – 5.57) ☐

Low Risk **Below 20 points:** Risk of GI complications is *not significantly increased* (0.4%-2.8%) by taking NSAIDs if taken as recommended.

High Risk **20 points and above:** Risk of GI complications is *significantly increased* (2.8%+) by taking NSAIDs. Consultation with a medical professional is advisable.

If condition 1 is not met, COX-2 inhibitors will be approved for use if any of the following conditions are met:

- In RA, patient has failed or is intolerant to either salsalate or choline magnesium trisalicylate.
- In OA, patient has failed or is intolerant to salsalate, choline magnesium trisalicylate, or acetaminophen.
- In primary dysmenorrhea, patient has failed or is intolerant to ibuprofen, naproxen, or other NSAID.
- In acute pain, patient has failed or is intolerant to one formulary narcotic analgesic.

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COX-2 = cyclooxygenase-2; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis. A scoring tool such as this could be used by physicians to assess a patient's risk of deep vein thrombosis.

years. In 2000, the average cost for thrombosis-related treatment for each of these patients was $2595, and the total cost of treatment, including costs related to the treatment of thromboembolic events and other comorbid conditions, averaged $58,752. In addition, the average pharmacy costs per patient were $1267, for an average per-patient total cost of treatment of $60,019. This cost reflects the serious underlying comorbid conditions present in these patients. The total cost of treatment for all 6477 patients with thromboembolic events was $389 million in 2000.

There may be opportunities to greatly improve the quality and overall cost effectiveness of the care of these patients. If there is significant variation in patient treatments, physicians can target some patients for more optimal management. It is the responsibility of the physician and the health plan to work together for the accurate assessment and optimal management of these patients.

Among patients covered by Prescription Solutions, 83% are receiving enoxaparin, 9% are receiving standard heparin, 7% are receiving framycetin, and less than 1% are receiving tinzaparin.

Research Opportunities in DVT

There are several significant research opportunities in the areas of DVT prevention and treatment. It is a high-cost condition, and those with DVT often also have significant comorbid conditions, as shown by the analyses described above. Additionally, there is significant variation in the way that DVT is managed.

One such opportunity is the development of a pharmacy-based model to predict DVT. A retrospective database study could be used as the basis for the model, which would be used both to identify patients who may be at risk for DVT and to determine their level of risk. Those at significant risk for DVT would be candidates for early intervention such as LMWH prophylactic therapy. The patient's physician would be notified of the patient's status and would be asked to evaluate the patient for DVT or prophylactic therapy at the next office visit. The impact of this intervention would be measured by determining whether the incidence of DVT among this group of patients was actually lower as a result of the intervention.

Another research opportunity is the development of a scoring tool that could be used by physicians to assess a patient's risk of DVT. A retrospective database study could be used to develop the tool, which would identify appropriate candidates for DVT prophylaxis based on a reasonable risk threshold. The outcomes of patients identified by this tool and subsequently given DVT prophylaxis would then be compared with the predicted outcome for these patients without the use of the scoring tool.

Prescription Solutions has already developed one such tool and uses it to help identify candidates for cyclooxygenase-2–specific inhibitor therapy (**Figure 3**). Patients who were taking nonsteroidal anti-inflammatory drugs were first assessed to determine their risk for gastrointestinal bleeding. A risk score was developed using beta coefficients from a linear regression model. Those with a diagnosis of either osteoarthritis or rheumatoid arthritis were given a score of 6.4. Patients were also given a score for age, with older people receiving higher age scores. Patients previously hospitalized for gastrointestinal bleeding were given a score of 18 on this risk factor. Scores were also given for risk factors such as taking steroid medications and current use of warfarin or other anticoagulant medication. Patients with a total risk score of 20 or higher were designated as being at high risk for gastrointestinal bleeding, and therefore, as being good candidates for therapy with a cyclooxygenase-2–specific inhibitor.

Another research opportunity in the area of DVT is confirming the appropriateness of LMWH prophylaxis for the medically ill. A prospective, randomized, naturalistic study could be performed to identify medically ill patients who would be appropriate candidates for LMWH prophylaxis. This information would be shared with the patients' physicians, who

would be asked to evaluate the patients to determine whether they are appropriate candidates for outpatient DVT prophylaxis. The impact of this intervention would then be measured.

Conclusion

There is significant evidence that DVT is a potentially devastating and very costly condition. Strategies are being devised to identify patients who might benefit from prophylaxis and to alert their physicians about the importance of this approach. A pharmacy-based DVT predictive model, developed through the use of a retrospective database study, is one such strategy. In addition, a scoring tool could be developed and used by physicians to assess patients' risk of DVT. These strategies will be formulated and implemented carefully to optimize their effectiveness.

··· DISCUSSION HIGHLIGHTS ···

Cost Estimation

Dr. Thapar: How do you determine those medical costs?

Dr. White: We have access to pharmacy and medical data for the entire population that we manage.

Dr. Thapar: Then you're basically taking the encounter data and plugging in what Medicare paid for the current procedural terminology (CPT) code. Is that correct?

Dr. White: It depends. For the shared-risk data or the hospital-based claims, we use the actual amount paid by the plan, the shared-risk arrangement. For the outpatient claims that are in a predominantly capitated environment, we use the submitted amount, or the amount that the group asked us to pay, or what their actual cost would have been. So, the information came from 2 sources, depending on whether there was a hospital claim or a professional encounter claim. We recognize that the cost data may not be the true cost of care but it helps give us an estimate.

Dr. Thapar: You cannot determine the cost from the outpatient side or from the inpatient professional. For your inpatient facility, you can use your per diem payments, but you cannot extrapolate cost information from the data submitted by the independent practice associations or by medical groups because they are not paid on a fee-for-service basis. They submit encounter data to you, and you basically have to extrapolate from that how much it would have been based on the CPT code. There is no other way you can plug in medical costs otherwise.

Dr. White: Absolutely, and you bring up a good point, because there are limitations, but keep in mind that the professional encounter claims account for a very small percentage of the total costs. Hospital-based institutional claims account for most of the cost. It's important to understand the limitations, but nevertheless it's valuable information, and it gives us significant insight into how much it costs to treat patients with DVT, especially if you want to compare costs of treatment across other conditions.

Dr. Wales: Given that you have these data, and you know the total cost, can you run an analysis to find out what comorbid conditions are present in these patients? I would assume that information would play into your definition of the medically ill patient who might be a candidate for treatment.

Dr. White: Absolutely.

Dr. Wales: Have you done that analysis?

Dr. White: No. We're engaged in those discussions right now. These are the approaches that we'll be taking to better manage this population, but you're right. These patients have a lot of comorbid conditions and other issues that probably need to be addressed as well. It would be good to understand what comorbid conditions are present and what incre-

mental plan impact those conditions have in terms of cost.

Risk-Prediction Tools

Dr. de Lissovoy: Your risk-prediction tools are also very interesting. This, of course, is of great interest to managed care organizations. Their interest is to identify potentially high-cost members and get them in a case management program. Typically, though, risk-prediction instruments are very sensitive but not very specific. You discussed a pharmacy-based predictive model. Your access to laboratory data would seem invaluable in making accurate predictions. Do you plan to include these data in your model?

Dr. White: We would like to. The problem with incorporating the laboratory data into the predictive model on a regular basis is that whatever data you run through the model should be consistent with the data that were used to develop the model. Typically, if we're working with a client, a medical group, or someone else, they don't have the laboratory data readily available in a format that can be used with the model. Pharmacy data are very standard and very easy to work with. We don't know how the incremental impact of adding the laboratory data would affect the model. Intuitively you would think that it would contribute to the predictive ability of the model. The pharmacy-based model has done very well for us so far, although, as you mentioned, it is a little bit more difficult to predict individual patients. We do understand what the positive predictive value is, however, and what the model can and cannot do.

Scoring Tool

Dr. White: From a physician's perspective, if you received a letter like the one we discussed earlier, and you had patients who were identified as being at sufficient enough risk threshold to warrant intervention, perhaps at that point you would evaluate those patients and consider prophylaxis. How would that be perceived?

Dr. Tapson: The bottom line is that it might be a lot of work for someone to call those patients and get them on appropriate prophylactic therapy. Sometimes by the time you reach the patient, he or she doesn't need the therapy anymore or is already receiving therapy. But I think it's useful information. If someone called me and told me that 100 of my patients needed prophylaxis, I would welcome the information. I would hope it was confidential information, and I would try to get the nurse-coordinator to look into it.

Dr. Michota: I think the kind of letter that probably goes to the physician is an FYI letter. I think that the letter really needs to go to the patient. The responsibility has to be on the patient to seek out his or her doctor. It becomes unbelievably problematic to send a letter to physicians telling them to bring in a large number of their patients for follow-up and prophylaxis.

Dr. Wales: I agree. The letter should say, "This is an FYI. File this. The next time you see the patient, review these things and do that." It should not describe a particular follow-up regimen. I don't think that we're sophisticated enough to drill down on a specific disease state on an outpatient basis and make a definitive recommendation regarding specific patients and their conditions. We really can only recommend general guidelines for the disease state for the physicians to use with their patients.

Dr. Witter: Do you think it would be better to send out this type of information without such patient-specific information? It could alert physicians to issues that should be considered in all patients with DVT.

Dr. Tapson: I think sending a letter like that to physicians to make them consider prophylaxis in some patients is a good idea, and it doesn't put the physician on the spot. We want what's best for our patients, and that's why I think that the FYI letter might be useful. It doesn't really put physicians on the spot.

Dr. Michota: Yes. And the other thing you

can use in such a letter is soft language. That is always good when you are dealing with physicians, because nobody likes to feel they are being told what to do. Perhaps the letter could be framed with a real-life example of how someone incorporated the information into practice and how patient care is being improved.

Dr. White: Possibly, a pilot study or program could be carried out to get some historical experience, which could be shared with physicians in the letter.

Dr. Michota: You could very easily do a simple, facilitated, focus-group study with a cross-section of physicians. You would show them the letter you are thinking about sending and get their reactions to it.

Dr. Hoffman: It's a question of education. Rather than sending out a threatening letter or a letter that could lead to legal action, I think we should try to educate physicians. We tell them, "This is what you do if you have a patient who fits this risk-prediction model of DVT."

Dr. Thapar: If anything is more unpredictable than the fairer sex it is trying to understand what makes physicians follow guidelines, or for that matter, not follow guidelines. With that disclaimer I will go out on a limb and say that sending a letter out to the physicians that says, "Consider prophylaxis in these patients" will not work well. We already have well-established guidelines and yet many physicians are not adhering to them.

In my experience, guidelines work better when they are simple, clear, evidence based, and approved by local thought leaders in the physician community. We need to provide local physicians with evidence that prophylaxis works and they will come up with the same guidelines to endorse it. Having a general meeting with providers, discussing these guidelines, and getting their input and buy-in also goes a long way.

However, there is more than one way to skin a cat and some of the other suggestions may work just as well; what is important is understanding the needs and wishes of local physicians.

Dr. White: What about giving the physicians a scoring tool that's been tested and validated? Would that be useful?

Dr. Michota: If there's 1 area of medicine where we've got lots of scoring tools, it is preoperative evaluation. Adding up the points doesn't really do much for me as a physician unless I've got a lot of other healthcare providers who work for me writing down the points for me. It's got to be brought down to 7 very discrete things. In the best models, each variable is 1 point. But when I'm looking at your sheet, with 6 points, 9 points, I'm thinking, there's no way I would ever use something like this. I would just use common sense based on the variables. It's got to be very simple, or if it's complicated, somebody else has to do it.

··· REFERENCE ···

1. Prescription Solutions. Data on file.