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- Subject Reviews
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Paris in the fall—a time when nature’s vibrant colors rival those found on French artists’ palettes. Edouard Cortès (1882-1969) was one such artist who captured the beauty of an autumnal Parisian flower market in his painting Flower Stalls by the Madeleine. As a Naturalist painter with an Impressionistic flair, he used splashes of color for the fall leaves and fresh flowers and bold strokes of paint for the figures, awnings, and buildings. Although it would seem that Cortès painted in a casual manner, he actually applied the paint very carefully and deliberately to achieve his desired effect.

Cortès invites the viewer into the setting depicted in Flower Stalls by the Madeleine with his use of warm hues and compelling perspective. It is a timeless scene brought to life by a multitude of vivid colors and high contrasts of light and dark tones. There is a pleasant symmetry to the painting, as the tall trees on the left side of the artwork echo the vertical columns on the right. Cortès skillfully balanced the verticals with the horizontal direction of the flower-stall awnings. The centrally focused composition is dominated by a bright red awning that serves to draw the eye to the flowers beneath it and then to the passersby. Most of the people seem interested in the flowers in one way or another—some are simply observing their beauty while others are selecting a bouquet. One can imagine the gentleman in the foreground thinking about buying some flowers for his wife to brighten their home.

Cortès was born into an artistic family in August 1882 in Lagny-sur-Marne, a small town located about 20 miles east of Paris. His grandfather, André Cortès, was renowned for his work on the stained glass windows of the Cathedral of Seville, and his father, Antonio Cortès, was a painter for the Spanish Royal Court. According to his biography on the Artnet Web site: “In this artistically conducive atmosphere, Edouard showed exceptional talent early and decided at a young age that he was destined to be a painter. He once stated, ‘I was born from and for painting.’”

Cortès trained at his father’s studio and was influenced by his brother, who was also a painter, as well as other local artists. Before he began his formal art training, 16-year-old Cortès was lauded as “the young phenomenon of the French art scene” when his large painting Le Labour was shown at the national exhibition of the Société des Artistes Français in Paris in 1899.

Further information about Cortès’s growth as an artist is provided by the Royal Alberta Museum’s Web site: “…at 17, Cortès began formal studies at the École des Beaux-Arts [the national French art school in Paris] where, for five years, he studied the genres of Classical and Impressionistic art. Living in the heart of Paris, Cortès was surrounded by famous landmarks such as Notre Dame, the Opéra, the Arc de Triomphe, the Champs-Elysées, the Eiffel Tower, and the Church of Sainte Madeleine (which was undoubtedly among the artist’s favorites). Inspired by these monuments, he painted them from different points of view, at certain times of the day, and in varying seasons.”

The affection Cortès felt for Paris, the “City of Light,” was the inspiration for his paintings. Often called a painter of light, Cortès’s skill is particularly evident in his evening compositions—windows glow within their murky surroundings, and luminous streetlights are reflected on the glistening streets, wet from a nocturnal rain. His Parisian street scenes were in great demand by both collectors and the general public. Flower Stalls by the Madeleine is one of several variations of this locale that he painted.

Cortès married Fernande Joyeuse in 1914, and their child, Jacqueline, was born two years later. Fernande died in 1918, and he subsequently married her sister, Lucienne. He often included his wife and daughter in the foreground of his paintings. In the mid-1920s, Cortès and his family moved to the country, and he began painting scenes of rural life. During this period, he received many awards, gained great notoriety, and was a frequent exhibitor at the major art salons in Paris.

In 1928, Cortès’s fame increased when 30 of his paintings were exhibited in Toronto, Winnipeg, and Montreal, Canada. His beautiful depictions of Paris were now accessible to markets outside of Europe. These scenes were always popular, and he continued to paint them until his death in 1969.

In mid-2001, a retrospective of Cortès’s work titled “Edouard Cortès (1882-1969): Paris and the French Countryside Revealed” was held at the Royal Alberta Museum’s Provincial Museum of Alberta in Edmonton, Alberta, Canada. “Paris,” “Landscapes,” “Interiors,” and “Creative Influences” were the exhibition’s themes. The work of 19 other artists who captured the splendor of Paris and the French countryside from the mid-19th to early-20th century accompanied the exhibition. Pierre-Auguste Renoir and Pierre Montézin, Cortès’s close friend, were among the featured artists.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCES
www.artnet.com
http://www.royalalbertamuseum.ca/gallery/retro/cortes.htm
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REFERENCE

ABSTRACT

OBJECTIVE: Inappropriate antibiotic use is a well-recognized public health problem because of its association with the emergence of resistant bacteria. It also is a source of unnecessary health care costs and of potentially severe adverse drug reactions. Although there are no evidence-based indications for the use of antibiotics in the treatment of asthma in the absence of comorbid bacterial conditions, physicians might feel more pressure to prescribe them to children with this chronic disease. The objectives of this study were to (a) determine if antimicrobial prescription utilization rates are higher for pediatric patients with asthma than a matched comparison group and (b) identify common variables (gender and age) that might explain higher antibiotic utilization rates in children.

METHODS: Using administrative claims data, we conducted a retrospective cohort study of children with asthma (age range 5 to 18 years) who were members of a large health plan from January 1, 2000, to December 31, 2002, in the southeastern United States. A comparison group was created that was matched according to age, sex, regional codes, and insurance product line. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to identify asthmatic patients (493.xx), as well as to link antibiotic prescriptions to diagnosis codes from claims for medical office visits.

RESULTS: Asthmatics consistently received significantly more services, including a mean of 1.74 (SD 1.82) antibiotics per patient per year (PPPY) compared with a mean of 0.96 (SD 1.32) antibiotics PPPY for nonasthmatics (t = 25.71, P < 0.001). Asthmatics received antibiotics more often for all diagnoses. The more frequent receipt of antibiotics was true for conditions related to the respiratory tract (e.g., upper respiratory infection and bronchitis) as well as for conditions unrelated to the respiratory tract (e.g., urinary tract infection and acne). A diagnosis of asthma significantly increased the likelihood of a prescribed antibiotic by 26% to 86%.

CONCLUSION: This study demonstrated that pediatric asthmatic patients received significantly more antibiotic prescriptions than nonasthmatics for conditions caused by bacteria, as well as for conditions more likely to be viral in origin. In this era of concern about the widespread use of antibiotics and consequent antimicrobial resistance, further research needs to be conducted concerning the appropriateness of antibiotics in the treatment of asthma. Studies on the appropriate use of antibiotics in asthma could help reduce the overall use of antibiotics in children.

KEYWORDS: Children, Asthma, Antibiotics

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Authors

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Inappropriate antibiotic use is a well-recognized public health problem because of its association with the emergence of resistant bacteria. It also is a source of unnecessary health care costs and of potentially severe adverse drug reactions. The Centers for Disease Control and Prevention (CDC) and other national organizations such as the American Academy of Family Physicians and the American Academy of Pediatrics actively promote judicious use of antibiotics in populations such as children who have a historically high rate of antibiotic use. In addition, previous studies have attempted to determine the patterns of behavior that influence the misuse of antibiotics by physicians.

The latest data from the National Ambulatory Medical Care Survey (NAMCS) did find decreasing trends in both the population- and visit-based antimicrobial prescription rates overall, and for respiratory tract infections for children and adolescents seen by office-based physicians. However, antibiotics were still prescribed inappropriately for diagnoses most likely due to viral infection such as colds, upper respiratory tract infection (URI), and bronchitis. Other studies in children and adults have noted similar misuse of antibiotics.

A diagnosis of asthma may further complicate the physician’s decision to use or not use antibiotics for respiratory tract infections. Although there are no evidence-based indications for the use of antibiotics in the treatment of asthma in the absence of comorbid bacterial conditions, physicians might feel more pressure to prescribe them to children with this common chronic disease. However, the National Asthma Education and Prevention Program Expert Panel Report, “Guidelines for the Diagnosis and Management of Asthma, Update on Selected Topics 2000,” states, “Antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions—e.g., for those patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis.” In addition, patients with asthma might present to the physician more often with respiratory complaints.

The objectives of this study were to (a) determine if antimicrobial prescription utilization rates are higher for pediatric patients with asthma than a matched comparison group and (b) identify common variables (gender and age) that might explain higher antibiotic utilization rates within specific diagnostic categories between children.

Methods

We conducted a retrospective cohort study in the southeastern United States of children with asthma (age range 5 to 18 years)
who were enrolled in a large health plan, including indemnity, preferred provider organization (PPO), and health maintenance organization (HMO) lines of service, from January 1, 2000, to December 31, 2002. To be included, all patients had to be continuously enrolled for at least 2 years and have pharmacy benefit coverage. Total enrollment in the health insurance plan is measured according to the number of members enrolled as of December 31 of each year. The HMO/point-of-service (POS) line of business had 579,567 enrolled in 2000, 659,314 enrolled in 2001, and 735,502 enrolled in 2002. The PPO line of business had 447,446 enrolled in 2000, 554,775 enrolled in 2001, and 740,717 enrolled in 2002. Continuous enrollment is defined as being enrolled in the health plan for at least 24 months without gaps in coverage.

Asthmatic patients were identified if they had 1 of the following: (a) 1 hospitalization or 1 visit to the emergency department with an asthma code (Common Procedural Terminology [CPT] 493.xx); (b) 2 or more outpatient visits with a 493.xx code; (c) 2 or more pharmacy claims for the following medications: inhaled fluticasone/salmeterol (Advair), inhaled triamcinolone (Azmacort), inhaled fluticasone (Flovent), inhaled budesonide (Pulmicort Turbohaler), inhaled budesonide (Pulmicort Respules), inhaled beta-agonist (Vanceril), inhaled albuterol, nebulized albuterol, oral albuterol, inhaled pirbuterol (Maxair), inhaled formoterol (Foradil), inhaled salmeterol (Serevent), oral zafirlukast (Accolate), oral montelukast (Singulair), inhaled Cromolyn, inhaled nedocromil, oral theophylline; or (d) 1 or more pharmacy claims for oral prednisolone and 1 of the above-listed medications. Patients could be identified by more than 1 criterion. Antibiotic use was identified by selecting National Drug Code (NDC) codes for antibiotics listed in oral forms in The Harriet Lane Handbook. Any antibiotic with only nonrespiratory indications was excluded from analysis (i.e., metronidazole and nitrofurantoin).

To control for the effects that age, sex, geographical region, or insurance product line may have had on prescribing rates of antibiotics in children with asthma, a comparison group was created matched according to age, sex, regional codes, and insurance product line (indemnity, PPO, or HMO). Regional codes indicate specific “local market” areas. Each region code represents a specific geographic area of the state of Georgia. Each member’s region code is based on his or her place of residence. Product line provides an indication of the member’s benefit structure. The International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes\(^9\) (ICD-9-CM) for the 5 respiratory tract infections studied were (1) otitis media, 381.0, 381.4, 382.0, 382.4, and 382.9; (2) pharyngitis, 034.0, 462, and 463; (3) sinusitis, 461 and 473; (4) bronchitis, 466.0 and 490; and (5) URI, 465, and common cold, 460. These are the same codes identified in the NAMCS data. A second category, including pneumonia (480-486), urinary tract infection (UTI; 595.0, 595.9, and 599.0), chlamydial cervicitis (099.53), gonococcal cervicitis (098.15), and acne (706.1), was also included in the analysis as an attempt to link antibiotic use with other diagnoses for which antibiotics are appropriate.

Visit codes were considered to be linked to an antibiotic fill if the medical visit was in the range of 5 days prior to or 1 day after an antibiotic fill. If more than 1 diagnosis was recorded for an encounter, we assigned a primary diagnosis, giving priority to a potential bacterial source. (For example, if URI and otitis media were coded, the latter was designated “primary.”) All follow-up and medical visits not in the range of 5 days prior or 1 day after an antibiotic fill were excluded from analysis.

### Statistical Analyses

All variables reflect rates or means per patient per year (PPPY) due to the fact that subjects had varying lengths of time for which claims data were available in the 3-year period. Each rate or mean PPPY was determined using a weighted average of each subject’s data over 3 years. Rates and sums were determined for each year and the corresponding number of months the subject contributed data to a particular year. The weights were the inverse of the number of months per year per subject. Thus, the weighted average of each rate or mean across the 3 years was calculated using the total number of months with available data as the denominator for each subject. Descriptive statistics were calculated on all variables. To examine univariate differences between asthmatics and nonasthmatics in demographics (sex, marital status of home, and line of business), utilization (inpatient, outpatient, and office and emergency room visits), paid costs (total, facility, provider, and prescription), number of inappropriately prescribed antibiotics, number of appropriately prescribed antibiotics, and any prescribed antibiotic overall and by diagnosis, chi-square tests or t tests were used.

Logistic regression was used to examine age, sex, asthma status, the interaction between age and asthma status, and the interaction between sex and asthma status on each of the diagnoses of interest for which an antibiotic was prescribed. Data were analyzed using SAS statistical software (SAS version 8.2), and statistical significance was assessed using an alpha level of 0.05.

## Results

The cohort included 5,856 asthmatics and 5,195 nonasthmatics. Of the 5,856 asthmatics, 748 (12.8%) had at least 1 inpatient or emergency room visit with an ICD-9-CM code for asthma, 2,415 (41.2%) had 2 or more outpatient visits with an ICD-9-CM code for asthma, 5,061 (85.7%) had 2 or more pharmacy claims for the specified asthma medications, and 435 (7.4%) had 1 or more pharmacy claims for oral prednisolone and 1 of the specified asthma medications. Patients could have more than 1 indication category for asthma (e.g., 1 inpatient visit with an ICD-9-CM code for asthma and a pharmacy claim for...
for 2 or more of the specified medications); thus the percentages of patients with individual criteria exceed 100%.

The gender distribution was similar for both populations (asthmatics 41.6% female and nonasthmatics: 42.2% female). Age distribution was also similar between the 2 groups (Table 1). Table 2 lists the 4 inclusion criteria and how many patients within the study cohort fell into each category. The inclusion criteria were not mutually exclusive, and there were patients who were retained by more than 1 inclusion criterion.

Table 3 reports the average use of selected health care services. Asthmatics consistently received significantly more services, including a mean of 1.74 (SD 1.82) antibiotics PPPY compared with a mean of 0.96 (SD 1.32) antibiotics PPPY for nonasthmatics (t = 25.71, P < 0.001). Specifically, female asthmatics were prescribed a mean of 1.88 (SD 1.88) antibiotics and male asthmatics were prescribed a mean of 1.63 (SD 1.78) antibiotics, while control females were prescribed 0.97 (SD 1.26) antibiotics and control males were prescribed 0.96 (SD 1.36) (analysis of variance [ANOVA] F (normal distribution function [ndf]=1, desirable degrees of freedom [ddf]=11,050) for interaction between asthma and sex = 13.94, P < 0.001) Asthmatic females had significantly higher mean numbers of antibiotics prescribed than all other groups (Tukey-Kramer adjusted P < 0.001 for each pair-wise comparison) and asthmatic males had significantly higher mean numbers of antibiotics prescribed than control females (Tukey-Kramer adjusted P < 0.001) and control males (Tukey-Kramer adjusted P < 0.001). Control male and female patients did not have significantly different mean numbers of antibiotics prescribed (Tukey-Kramer adjusted P = 0.988).

Primary diagnoses related to the prescription of antimicrobial agents are presented in Table 4. The upper half of the table shows that for all diagnoses of interest in this study, other than chlamydia, individuals with asthma were significantly more likely to fill a prescription for an antibiotic than were those individuals without asthma. The last line of the table shows that individuals with asthma were also more likely to fill a prescription for an antibiotic for the all diagnoses other than those specifically included in the study. The lower half of Table 4 shows that individuals with asthma were more likely to have an episode of health care with a diagnosis of URI, bronchitis, sinusitis, and pneumonia and not fill a prescription for an antibiotic.

Table 5 gives the logistic regression results for each of the diagnoses for which an antibiotic was prescribed, examining age, sex, asthma status, the interaction between age and asthma status, and the interaction between sex and asthma status. For URI, pharyngitis, and otitis media, there were no statistically significant interactions. For each of these models the main effects of age, sex, and asthma status were statistically significant, indicating that those with a diagnosis for which an antibiotic was prescribed were more likely to be female, more likely to have asthma, and less likely to be in the 11-to-14 age group compared with the 5-to-10 age group. For bronchitis, sinusitis, and pneumonia, significant interactions were detected, and thus the main effects cannot be interpreted. For bronchitis and sinusitis, a significant interaction between sex and asthma status was found, with those having a diagnosis for which an antibiotic was prescribed being more likely to be female asthmatics. A significant interaction between age and asthma

### TABLE 1 Baseline Characteristics of Asthmatics and Comparison Group*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthmatics</th>
<th>Nonasthmatics</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2,437</td>
<td>2,190</td>
<td>42.2</td>
</tr>
<tr>
<td>Male</td>
<td>3,419</td>
<td>3,005</td>
<td>57.8</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>2,204</td>
<td>2,000</td>
<td>38.5</td>
</tr>
<tr>
<td>11-14 years</td>
<td>1,919</td>
<td>1,684</td>
<td>32.4</td>
</tr>
<tr>
<td>15-18 years</td>
<td>1,733</td>
<td>1,511</td>
<td>29.1</td>
</tr>
</tbody>
</table>

* There were 5,856 persons in the asthmatics group and 5,195 in the nonasthmatics group.

### TABLE 2 Patient Inclusion Criteria

<table>
<thead>
<tr>
<th>Criteria Applied*</th>
<th>Number (%) of Patients Retained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identification of patients with at least 1 inpatient or emergency room visit with an ICD-9 code for asthma</td>
<td>748 (12.8)</td>
</tr>
<tr>
<td>2. Identification of patients with 2 or more outpatient visits with an ICD-9 code for asthma</td>
<td>2,415 (41.2)</td>
</tr>
<tr>
<td>3. Identification of patients with 2 or more pharmacy claims for specific asthma medications</td>
<td>5,061 (85.7)</td>
</tr>
<tr>
<td>4. Identification of patients with 1 or more pharmacy claim for oral prednisolone and 1 of the specific asthma medications</td>
<td>435 (7.4)</td>
</tr>
</tbody>
</table>

* Patients can be retained by more than one criterion. ICD-9 = International Classification of Diseases, Ninth Revision.

### TABLE 3 Prescription and Medical Visit Utilization for Asthmatics and Nonasthmatics per Patient per Year*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthmatics</th>
<th>Nonasthmatics</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of study years</td>
<td>2.85</td>
<td>2.92</td>
<td>0.23</td>
</tr>
<tr>
<td>Number of medical visits</td>
<td>5.70</td>
<td>2.94</td>
<td>3.26</td>
</tr>
<tr>
<td>Number of total pharmacy claims</td>
<td>9.14</td>
<td>3.50</td>
<td>5.38</td>
</tr>
<tr>
<td>Number of antibiotic claims</td>
<td>1.74</td>
<td>0.96</td>
<td>1.32</td>
</tr>
<tr>
<td>% of antibiotic claims</td>
<td>19.0</td>
<td>27.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pharmacy claims per medical visit</td>
<td>1.60</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Antibiotic claims per medical visit</td>
<td>0.31</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>

* There were 5,856 persons in the asthmatics group and 5,195 in the nonasthmatics group.
Antibiotics significantly more frequently than do pediatric
we have demonstrated that pediatric asthma patients receive
a diagnosis. When we could not link an antibiotic to a diagnosis,
the main effect for age can be examined. For both bronchitis and sinusitis,
age was significant, and those in the 11-to-14 age group were
less likely to have a diagnosis of bronchitis for which an antibiotic
was prescribed than those in the 5-to-10 age group. For pneumonia,
a significant interaction between age and asthma status
was found, with those having a pneumonia diagnosis for which
an antibiotic was prescribed being less likely to be asthmatics in
the 11-to-14 age group.

Discussion
We have demonstrated that pediatric asthma patients receive
antibiotics significantly more frequently than do pediatric
patients who do not have asthma. This includes receiving antibiotics appropriately for conditions such as otitis media and sinusitis, which are more likely to be caused by bacteria, but also receiving antibiotics inappropriately for conditions more likely to be viral in origin, such as URI, bronchitis, and the common cold. Additionally, pediatric patients with asthma presented to the physician more often with these complaints. This suggests that patients with asthma perhaps suffer more respiratory infections or that their parents bring them to the physician more often than nonasthmatics when they have respiratory complaints. Unfortunately, the data available for this study did not allow us to determine which of these 2 possible explanations was more probable.

We found higher antibiotic use among female subjects with asthma for all the respiratory tract diagnoses except for pneumonia (URI, bronchitis, pharyngitis, sinusitis, and otitis media). Previous studies have also noticed gender differences in asthma management. It has been suggested that girls with asthma may experience less wheezing and more night-time cough than boys and, therefore, may be treated more often for secondary diagnoses rather than receiving aggressive management of their asthma. Also, female patients report greater asthma-related hardship. They rate their intensity of symptoms higher than male subjects and report lower quality of life related to their asthma. These perceptions may influence how often they present to the physician and how often the physician prescribes antibiotics. Previous studies have documented that female subjects receive fewer inhaled steroids than male subjects, thus resulting in less treatment for the airway inflammation that underlies the disease. Of interest, middle-school-aged patients were often less likely to receive antibiotics than their older counterparts in our study.

Limitations
Although the validity of using ICD-9-CM codes to identify diseases of interest has been shown, and several similar studies have used data such as ours, there are limitations of our study related to the use of coding data. The first limitation is the high number of antibiotics dispensed that we could not link to a diagnosis. When we could not link an antibiotic to a diagnosis, we could not include the event in our analyses. However, more antibiotics were given to asthmatics than nonasthmatics, reflecting the patterns seen when antibiotics were associated with a diagnosis. Also, we do not know if any antibiotics were prescribed that were filled without a pharmacy claim being filed. We feel that few antibiotic prescriptions were filled without a payment claim, but we have no way to verify this opinion.

An additional limitation of our study was the use of matching for potential confounding variables that may have resulted in our control population's differing from the population of all children who do not have asthma. Additionally, our population only includes 1 group of children insured by a single company.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthmatics (N = 5,856)</th>
<th>Nonasthmatics (N = 5,195)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antibiotic prescribed</td>
<td>4,343</td>
<td>74.2</td>
<td>2,796</td>
</tr>
<tr>
<td>URI</td>
<td>1,831</td>
<td>31.3</td>
<td>937</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1,701</td>
<td>29.1</td>
<td>574</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2,976</td>
<td>50.8</td>
<td>2,062</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2,324</td>
<td>39.7</td>
<td>1,174</td>
</tr>
<tr>
<td>Otitis media</td>
<td>1,575</td>
<td>26.9</td>
<td>1,006</td>
</tr>
<tr>
<td>UTI</td>
<td>336</td>
<td>5.7</td>
<td>192</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>1</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>495</td>
<td>8.5</td>
<td>352</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>744</td>
<td>12.7</td>
<td>298</td>
</tr>
<tr>
<td>Antibiotic prescribed for diagnosis‡</td>
<td>4,235</td>
<td>72.3</td>
<td>2,695</td>
</tr>
<tr>
<td>URI</td>
<td>1,820</td>
<td>41.9</td>
<td>943</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>869</td>
<td>20.0</td>
<td>255</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2,313</td>
<td>53.3</td>
<td>1,494</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1,024</td>
<td>23.6</td>
<td>465</td>
</tr>
<tr>
<td>Otitis media</td>
<td>710</td>
<td>16.4</td>
<td>483</td>
</tr>
<tr>
<td>UTI</td>
<td>266</td>
<td>6.1</td>
<td>152</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>1</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>444</td>
<td>10.2</td>
<td>304</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>555</td>
<td>12.8</td>
<td>229</td>
</tr>
</tbody>
</table>

Note: An individual could potentially have multiple medical claims for the same diagnosis during the 3-year study time period. For each of these medical claims, an antibiotic may or may not have been prescribed.

* The number of individuals with at least 1 medical claim for each diagnosis during the study time period for which an antibiotic was prescribed.
† The number of individuals with at least 1 medical claim for each diagnosis during the study time period for which an antibiotic was not prescribed.
‡ The number of individuals with at least 1 medical claim for each diagnosis during the study time period for which an antibiotic was prescribed.
CI = confidence interval; Rx = prescription; URI = upper respiratory infection; UTI = urinary tract infection.
in 1 state; thus, our results may not be generalizable across the country. Also, within our study group of patients we were not able to obtain demographic data on race, socioeconomic class, or urban versus suburban residence, all of which are known to affect asthma rates and care. However, we did attempt to minimize demographic differences between our patients and the control group by matching for insurance type and regional codes (regional divisions within the state assigned by the managed care organization). We also were not able to estimate the severity of asthma in each patient. It is possible that there are subgroups of asthmatics that are responsible for the majority of the increased use of antibiotics. Unfortunately, the limitations of the data source (administrative claims) did not allow us to meaningfully subdivide the study subjects further.

**Conclusion**

This research, using administrative medical and pharmacy claims, found that asthmatic children are significantly more likely to receive antibiotics than their nonasthmatic counterparts and that girls with asthma receive more antibiotics than boys. This conclusion adds weight to the concern about the widespread use of antibiotics and subsequent resistance. Our study did not address the indications for antibiotic use in children with asthma or the reasons that antibiotics are prescribed more often for patients with asthma. While we found a higher rate of use of antibiotics in children with asthma, we are not able to determine if these antibiotic pharmacy claims represent either appropriate or inappropriate use. Also left to future research is identification of the interventions that should be instituted to decrease inappropriate antibiotic use in pediatric asthmatic patients. Since asthma is so common, guidelines on the appropriate use of antibiotics in asthma may help reduce the overall use of antibiotics in children.

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**DISCLOSURES**

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Stallworth served as principal author of the study. Study concept and design were contributed by Stallworth, Fick, and Ownby. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was primarily the work of Stallworth and Waller, and its critical revision was the work of all authors. Statistical expertise was contributed by Waller, and administrative, technical, and/or material support was provided by Denise Hodo (see Acknowledgment).

**REFERENCES**


Antibiotic Use in Children Who Have Asthma: Results of Retrospective Database Analysis


Longitudinal Evaluation of Health Plan Cost per Venous Thromboembolism or Bleed Event in Patients With a Prior Venous Thromboembolism Event During Hospitalization

MICHAEL F. BULLANO, PharmD; VINCENT WILLEY, PharmD; OLE HAUCH, MD; GAIL WYGANT, MS, RN; ALEX C. SPYROPOULOS, MD; and LAUREN HOFFMAN, PharmD

ABSTRACT

OBJECTIVE: To measure the per-event health plan costs for acute and follow-up treatment not directed by a clinical study protocol in a group of commercially insured patients in 2 managed care organizations following an incident hospitalization that included a diagnosis for a venous thromboembolism (VTE) event.

METHODS: A cohort of patients with an incident in-hospital VTE event, consisting of deep vein thrombosis (DVT), or pulmonary embolism (PE), or both DVT + PE, was retrospectively identified from the administrative claims databases of 2 large U.S. health care plans. Inclusion criteria were (a) an inpatient VTE event between January 1, 1998, and December 31, 2000, (b) no VTE diagnosis or anticoagulation therapy 3 months prior to the incident VTE in-hospital event, (c) at least 1 anticoagulation pharmacy fill following the incident hospital VTE, and (d) continuous health plan enrollment 3 months prior to and 6 months following the incident hospital VTE event. Total costs were reported on a per-event basis and consisted of the aggregated amount paid by the health plan to the provider after subtraction of member cost-share. Costs were collected separately, first for the incident VTE event for all patients identified and second for patients who had at least 1 of the following events in the follow-up period: bleed requiring or not requiring hospitalization, a recurrent VTE event requiring hospitalization, or a recurrent VTE and bleed (VTE + bleed) event requiring hospitalization. Costs were compared between incident diagnosis groups using multivariate generalized linear model techniques.

RESULTS: A total of 2,147 patients (DVT = 1,499 [69.8%], PE = 373 [17.4%], DVT + PE = 275 [12.8%]) were identified (mean age = 61.6 ± standard deviation [SD] 16 years; 46.3% male) and were followed for an average of 21.3 (median, 19.2) months. Disease severity was high in these patients, including 59.2% with a history of or active malignancy. The prevalence of VTE was 2.04 per 100,000 study-eligible health plan members. For the incident VTE events, average costs were $7,712 ± $16,339 (median, $3,131) per incident DVT event; $9,566 ± $13,512 (median, $6,624) per PE incident event; and $12,200 ± $24,038 (median, $6,678) per incident DVT + PE event. Warfarin treatment following the incident VTE event was administered to 97.3% of patients for an average of 6.7 (median, 5.0) months at an average cost of $19.40 per patient per month. During the average period of 21.3 months, 534 patients (24.9%) experienced an average of 1.24 bleed or recurrent VTE events per patient that required hospitalization at a mean cost of $14,975 per event or $2,101 per patient per year. For patients with a bleed in the follow-up period that required hospitalization, average costs were $12,326 ± $24,448 (median, $5,736) per recurrent VTE; $15,339 ± $52,029 (median, $4,999) per bleed; or $24,085 ± $65,411 (median, $10,185) per recurrent VTE + bleed event. During the follow-up period, a total of 612 patients (28.5%) experienced 1,489 recurrent bleed events that did not require hospitalization, at an average cost of $239 ± $386 (median, $95) per event. There were no significant differences in mean total costs for all pair-wise comparisons between the 3 incident diagnosis groups.

CONCLUSIONS: Of patients who experienced a VTE event during the incident hospital stay for any diagnosis, 1 in 4 experienced an average of 1.24 bleed or recurrent VTE events that required hospitalization in the 21 months of follow-up and incurred an average health plan cost of $14,957 per event. These data may be of interest to managed care decision makers when evaluating the cost impact of new therapies or providing more comprehensive anticoagulation management services for existing therapies.

KEYWORDS: Anticoagulants, Thrombosis, Thromboembolism, Pulmonary embolism, Deep vein thrombosis, Outcomes research, Retrospective study, Managed care, Cost

Pulmonary embolism (PE) and deep vein thrombosis (DVT), collectively known as venous thromboembolism (VTE), are significant causes of disability and death in the United States, resulting in approximately 300,000 hospitalizations and at least 50,000 deaths per year.1-3 It is estimated that direct medical care alone costs the country’s health care systems at least $600 million annually.4 In addition, among patients adequately treated for VTE, thromboembolism may recur in 5% at 3 months and up to 30% at 8 years.5-7 It has been suggested that, in DVT patients alone, nearly $500,000 in health care costs could be prevented per 100 patients per year if patients were properly screened and treated, a process that may prevent high recurrent event costs.8-9 The primary short-term goals of DVT therapy are to avoid the advancement of existing thrombi, the development of fatal PE’s, and the early recurrence of thrombotic disease. The long-term treatment objective is to prevent delayed recurrence of DVT and PE (PE events as well as potential sequelae such as postphlebitic syndrome and pulmonary hypertension).9 Effective regimens for acute treatment include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or adjusted-dose subcutaneous heparin. For initial VTE, acute therapy should be followed by warfarin therapy for at least 3 months if warfarin therapy is not contraindicated. Growing understanding of treatment for VTE has led to guidelines—an initial set in 1998, updated in 2001,10,11. The 1998 and 2001 guidelines were similar with respect to the intensity of oral pharmacotherapy used in prophylaxis after a VTE event.

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Note: An editorial on the subject of this article appears on pages 704-08 of this issue.
However, the 2001 guidelines added the confirmation of LMWH preparations as replacements for UFH in venous thromboembolism.15

As health care systems continue to strive to reduce the rate of increase in overall health care expenditures, particularly the cost of hospital care, costs associated with both initial VTE care and follow-up care with related sequelae are becoming increasingly important to formulary and health policy decision makers.12 Emphasis is being placed on safe and effective, yet cost-efficient treatments that represent the interests of both the health care system and the patient.13 A number of cost-effectiveness analyses have outlined VTE inpatient and outpatient management costs,8,14,15 and others have outlined the cost-effectiveness of LMWHs, warfarin therapy, and unfractionated heparins16-19; however, little research exists evaluating the period following an incident VTE for recurrent VTE events, bleed events, or therapy monitoring in a real-world setting. This study was designed to follow a group of commercially insured patients in 2 managed care organizations (MCOs) following an incident VTE, measuring the costs for acute and follow-up treatment undirected by protocol.

Methods

Study Design and Location

We conducted a retrospective, observational cohort study covering the period from October 1, 1997, through September 30, 2001. Electronic medical and pharmacy administrative claims from 2 health plans located in the southeast and western United States, with approximately 3.5 million and 7.5 million covered members, respectively, were extracted and used in this study. The health plans were similar in overall benefit design, types of health insurance products offered, and administrative claim data elements available for analysis. Both health plans had an independent practice association structure that largely comprised a health maintenance organization (HMO) and, to a lesser extent, preferred provider organization (PPO) members and point-of-service members. Some providers (hospital and physicians) operated under a prearranged or capitated reimbursement structure. In addition, both plans offered a Medicare + Choice (now Medicare Advantage) benefit (for those aged ≥65 years). Neither health plan directly sponsored any specific programs or interventions targeting anti-coagulation therapy during the time period of this study.

Study Population

This study included all members of the 2 MCOs for whom administrative claims data included a hospital claim with a primary or secondary diagnosis for either a DVT and/or PE during a hospitalization for any cause that occurred between January 1, 1998, and December 31, 2000. We designated the incident (i.e., first) claim for a member during the study period as the index diagnosis. Diagnosis of inpatient DVT or PE was determined by the presence of (a) International Classification of Diseases, Ninth Revision (ICD-9) codes of 451.1x for DVT and 415.1x for PE, in position 1 (primary) or 2 (secondary); (b) universal billing (1992 revision UB-92) codes associated with an inpatient hospitalization (100, 101, or 110); and (c) at least 1 pharmacy claim for an anticoagulation medication (Generic Product Identifier [GPI] = 83)20 in the 30-day period following the index diagnosis.

Patients were excluded from the study if they had been diagnosed with a VTE or had used any anticoagulation therapy in the 3 months preceding the index diagnosis or if they did not have continuous MCO eligibility for at least 3 months prior to and 6 months following the index diagnosis.

For purposes of analysis, patients were assigned to 1 of 3 groups based on their index diagnosis. The DVT group included patients who had an index diagnosis containing only ICD-9 codes (451.1x) for DVT (but not for PE), the PE group included all patients with an index diagnosis containing only ICD-9 codes (415.1x) for PE (but not for DVT), and the DVT + PE group included patients with ICD-9 codes for both DVT and PE (415.1x, 451.1x). In addition, patient identifiers were masked to protect the identity of individual health information.

We followed patients longitudinally from the index diagnosis to the end of benefit eligibility or to the end of the study period (September 30, 2001), whichever occurred first. We collected baseline data from the index date back to the patient’s beginning of eligibility or the beginning of the study period (October 1, 1997), whichever occurred first. To further describe the case mix of our population, surrogate measures of disease severity were measured during the preindex period. Collected measures included the number of distinct medications filled (i.e., distinct by chemical entity) and the total amount paid for all pharmacy and medical claims (regardless of diagnosis) by the health plan. These surrogate measures represent a measure of the burden of comorbid diseases, and their utility has been explained and compared previously.21 In addition, we captured the prevalence of known independent risk factors for recurrent thromboembolism22 by reviewing all medical and pharmacy encounters over the observation period.

Following the index diagnosis, we documented all bleed and recurrent VTE events based on the appearance of ICD-9 codes in the MCO claims data. We used the “place of service” field to determine whether the medical service occurred in the hospital, with or without subsequent skilled nursing care but not including direct admission to a skilled nursing facility (SNF), or in an outpatient setting. Postindex events were categorized as (1) recurrent VTE events requiring hospitalization (no bleed codes observed), (2) bleed events requiring hospitalization (no VTE codes observed), (3) VTE and bleed (VTE + bleed) events requiring hospitalization (codes for both VTE and bleed observed), and (4) bleed events not requiring hospitalization (code for bleed observed; codes related to VTE may or may not
be observed). For each event of interest, the corresponding series of claim records were assembled and the respective amount paid per event was aggregated using the “amount paid” (by the health plan to the provider after subtraction of the member cost-share) field within the administrative claims database (i.e., the patients’ coinsurance, copayments, and deductibles were not included in any of the cost calculations).

Cost and Clinical Outcomes

The primary cost outcome was the aggregated cost per event from the “amount paid” field in those patients requiring hospitalization for such events. Secondary cost outcomes included (1) the cost of the index VTE event, (2) outpatient anticoagulation therapy and related monitoring costs, and (3) the costs of treating bleed events not requiring hospitalization. To be counted, a claim must have had at least 1 ICD-9 code for a bleed (Table 1). Medical claims that had dates of service that were separated by more than 1 day were counted as separate encounters. In addition, the patient must have been receiving anticoagulation therapy at the time of the bleed occurrence.

To examine determinants of the total cost of care for postindex events requiring a hospital visit, aggregated costs were broken into 5 resource centers based on the individual UB-92 code assigned to individual paid amounts. For hospital admissions that were paid on a prospective basis (i.e., per diem), costs for the individual resource centers were calculated by multiplying the percentage that the resource center charge contributed to the total hospital charge by the total amount paid. For example, if the hospital charged $6,000 and was paid $4,000 for the entire admission on a prospective basis, and the claim line for room and board showed a charge of $3,000, room and board would have contributed 50% of the total charge, and the cost for room and board would have been calculated to be $2,000.

Emergency department included all emergent and urgent care services (UB-92 range: 450-459); room and board included all costs related to critical care units, wards, nursing, monitoring, and supply costs (UB-92 range: 100-249, 279-299, 620-624, 700-770); diagnostic and laboratory included all laboratory and diagnostic tests, such as radiographic tests, Doppler ultrasound, computed tomography, resonance-based diagnostic tests, and peripheral vascular laboratory costs (UB-92 range: 300-359, 402-409, 610-619, 921); and pharmacy (Rx) included all medication costs, specific medications not specified, and intravenous supplies and administration (UB-92 range: 250-269). All paid amounts that contained UB-92 codes that did not fit any other category, including operating room, anesthesia, dialysis, oxygen, and professional fees, were designated as “other.”

Outpatient international normalized ratio (INR) tests were identified in the administrative medical claims data utilizing the Current Procedural Terminology (CPT) code of 85610, and the “amount paid” field was captured to represent the cost. All anticoagulant medication costs (warfarin, UFH, and LMWH) were identified from the pharmacy claims database utilizing the appropriate GPIs (starting with 83), and costs were assigned using the “amount paid” field. In these particular health plans, anticoagulant utilization and costs could not be ascertained from the medical administrative claims database for the inpatient setting because all pharmacy charges for a hospital admission were aggregated on a single claim for that hospitalization. The pharmacy administrative claims database was utilized solely to determine the anticoagulant costs for outpatient care because both plans covered claims for anticoagulants under the pharmacy benefit.

<table>
<thead>
<tr>
<th>ICD-9</th>
<th>Bleed Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>287.9</td>
<td>Unspecified hemorrhagic conditions</td>
</tr>
<tr>
<td>360.43</td>
<td>Hemorrhage, except current injury</td>
</tr>
<tr>
<td>362.81</td>
<td>Retinal hemorrhage</td>
</tr>
<tr>
<td>372.72</td>
<td>Conjunctival hemorrhage</td>
</tr>
<tr>
<td>374.81</td>
<td>Hemorrhage of eyelid</td>
</tr>
<tr>
<td>376.32</td>
<td>Orbital hemorrhage</td>
</tr>
<tr>
<td>430</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>431</td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>432</td>
<td>Other and unspecified intracranial hemorrhage</td>
</tr>
<tr>
<td>448.9</td>
<td>Other and unspecified capillary diseases</td>
</tr>
<tr>
<td>459.0</td>
<td>Unspecified hemorrhage</td>
</tr>
<tr>
<td>523.8</td>
<td>Other specified periodontal diseases</td>
</tr>
<tr>
<td>530.82</td>
<td>Esophageal hemorrhage</td>
</tr>
<tr>
<td>531.0</td>
<td>Acute gastric ulcer with hemorrhage</td>
</tr>
<tr>
<td>531.4</td>
<td>Chronic or unspecified gastric ulcer with hemorrhage</td>
</tr>
<tr>
<td>532.0</td>
<td>Acute duodenal ulcer with hemorrhage</td>
</tr>
<tr>
<td>532.4</td>
<td>Chronic or unspecified duodenal ulcer with hemorrhage</td>
</tr>
<tr>
<td>533.0</td>
<td>Acute peptic ulcer, unspecified site, with hemorrhage</td>
</tr>
<tr>
<td>533.4</td>
<td>Chronic or unspecified peptic ulcer, unspecified site, with hemorrhage</td>
</tr>
<tr>
<td>562.02</td>
<td>Diverticulosis of small intestine with hemorrhage</td>
</tr>
<tr>
<td>562.03</td>
<td>Diverticulitis of small intestine with hemorrhage</td>
</tr>
<tr>
<td>562.12</td>
<td>Diverticulosis of colon with hemorrhage</td>
</tr>
<tr>
<td>562.13</td>
<td>Diverticulosis of colon with hemorrhage</td>
</tr>
<tr>
<td>569.3</td>
<td>Hemorrhage of rectum and anus</td>
</tr>
<tr>
<td>578</td>
<td>Gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>596.7</td>
<td>Hemorrhage into bladder wall</td>
</tr>
<tr>
<td>599.80</td>
<td>Other specified disorders of urinary tract</td>
</tr>
<tr>
<td>782.7</td>
<td>Spontaneous ecchymoses</td>
</tr>
<tr>
<td>784.7</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>784.8</td>
<td>Hemorrhage from throat</td>
</tr>
<tr>
<td>786.3</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>852</td>
<td>Subarachnoid, subdural, and extradural hemorrhage, following injury</td>
</tr>
<tr>
<td>958.2</td>
<td>Secondary and recurrent hemorrhage as an early complication of trauma</td>
</tr>
</tbody>
</table>

ICD-9= International Classification of Diseases, Ninth Revision.
Longitudinal Evaluation of Health Plan Cost per Venous Thromboembolism or Bleed Event in Patients With a Prior Venous Thromboembolism Event During Hospitalization

**Anticoagulation Therapy and Monitoring**

Duration of anticoagulation therapy was captured for patients prescribed warfarin and/or outpatient LMWH therapy. Because the daily dose of warfarin therapy is changed frequently between individual prescription refills, conventional approaches of determining duration of therapy that incorporate only days supply and fill dates may not be accurate. Therefore, we employed the following logic to determine duration of therapy. The first warfarin prescription date was identified in the follow-up period. From this date, all pharmacy and laboratory claims were reviewed in the subsequent 42 days (6 weeks) for the presence of a warfarin prescription or a laboratory claim for a prothrombin time/international normalized ratio (PT/INR). We selected 6 weeks a priori based on a prior study evaluating the validity of this approach in determining continuous warfarin therapy. In that study, the concordance between the 42-day algorithm and actual continuous warfarin therapy was very high (κ = 0.84). If one of these conditions was met, the same process continued from the date of the new warfarin prescription or the PT/INR. This logic was applied to a patient’s records until both conditions were not met; the date of last warfarin fill or PT/INR was recorded. The duration of warfarin therapy was calculated from the date difference between the first and last warfarin prescriptions plus days supply of the last prescription or the date of the last PT/INR test, whichever was greater. Respective costs representing paid amounts to pharmacy providers were captured and aggregated.

Outpatient monitoring consisted of capturing the utilization and respective costs of PT/INR tests. Patient records that exhibited warfarin use were scanned for a CPT code of 85610 to denote the presence of a PT/INR test. Costs for antifactor Xa levels were not captured because of the lack of a distinct CPT code during the period of extracted data.

**Statistical Analyses**

Descriptive statistics included mean (± standard deviation [SD]) and median values for continuous data and relative frequencies for categorical data. Continuous variables were compared between index groups with analysis of variance (ANOVA) with the Scheffe test for multiple comparisons. This post hoc test was chosen because it is more stringent (i.e., less likely to commit an α error) as compared with other tests. Due to the non-normal distribution of the data, we also examined results from Kruskal-Wallis statistical analyses. Because our data set was large, results from the 2 tests were equivalent, and we have elected to provide the more commonly used ANOVA. Categorical variables were compared using Pearson χ² tests. Rates of INR use were created by dividing the total number of PT/INR tests by each individual’s time of observation following the index diagnosis. Rates were compared by calculating 95% confidence intervals using the Poisson Exact methodology. For these procedures, statistical significance was defined a priori at an α of <0.05.

To determine if costs for postindex events were different between index diagnoses, multivariate generalized linear model techniques were used. Because prior research supports the observation that cost data appear to follow a γ distribution, we modeled cost outcomes using a general linear model (GLM) with a log link and γ distribution. The 4 cost outcomes modeled were (1) recurrent VTE alone requiring hospitalization, (2) bleed events alone requiring hospitalization, (3) recurrent VTE + bleed events requiring hospitalization, and (4) bleed events not requiring hospitalization. Model covariates included index diagnosis, age, gender, presence of risk factors for thrombosis observed in any period, history of bleed in the 3 months prior to the index VTE, and number of distinct medications at baseline. Postindex observation time was not introduced into the model because costs were analyzed on a per-event basis. We fit general linear models with all variables with Wald P values <0.15 (after eliminating collinear variables). For the final estimating model, we retained the set of variables all having Wald P values <0.15 and the largest negative Bayesian Information Criteria score for the model. All statistical analyses were performed using STATA 7.0.

**Results**

**Population**

Table 2 shows the sample selection. A total of 2,147 patients were included in our study: 887 and 1,260 from the southeastern and western health plans, respectively, representing an incidence of approximately 57 per 100,000 study-eligible members in the southeastern health plan and 41.6 per 100,000 study-eligible members in the western health plan. Baseline characteristics appear in Table 3. Of the 2,147 patients, 1,499 (69.8%) had an index diagnosis of DVT, 373 (17.4%) had an index diagnosis of PE, and 275 (12.8%) patients had an index

---

**Table 2 Sample Selection**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number (%) of Patients Remaining</th>
<th>Number of Patients Dropped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients must have had at least 1 VTE diagnosis between January 1, 1998, and December 31, 2000</td>
<td>26,103 (100)</td>
<td>–</td>
</tr>
<tr>
<td>Patients must not have had a VTE diagnosis in the 3 months prior to their index date</td>
<td>25,784 (98.8)</td>
<td>319 (1.2)</td>
</tr>
<tr>
<td>Patients must not have been receiving an anticoagulation medication in the 3 months prior to their index hospital event</td>
<td>23,564 (90.3)</td>
<td>2,220 (8.5)</td>
</tr>
<tr>
<td>Patients must have been continuously enrolled in a health plan (for a period of 3 months prior to and 6 months following their VTE index date)</td>
<td>15,850 (60.7)</td>
<td>7,714 (29.6)</td>
</tr>
<tr>
<td>Patients must have been exposed to at least 1 fill of a VTE anticoagulation medication following their index date</td>
<td>2,147 (8.2)</td>
<td>13,703 (52.3)</td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism.
Longitudinal Evaluation of Health Plan Cost per Venous Thromboembolism or Bleed Event in Patients With a Prior Venous Thromboembolism Event During Hospitalization

### TABLE 3: Cohort Characteristics Stratified by Index Diagnosis (N = 2,147)

<table>
<thead>
<tr>
<th></th>
<th>DVT (n = 1,499 (69.8%))</th>
<th>PE (n = 373 (17.4%))</th>
<th>DVT + PE (n = 275 (12.8%))</th>
<th>Overall (n = 2,147)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western health plan</td>
<td>617</td>
<td>117</td>
<td>183</td>
<td>1,260</td>
</tr>
<tr>
<td>Southeastern health plan</td>
<td>822</td>
<td>256</td>
<td>92</td>
<td>887</td>
</tr>
<tr>
<td>Total</td>
<td>1,499</td>
<td>373</td>
<td>275</td>
<td>2,147</td>
</tr>
<tr>
<td>Male (%)</td>
<td>46.2</td>
<td>45.6</td>
<td>48.0</td>
<td>46.3</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>61.3 ± 16</td>
<td>64.4 ± 15*</td>
<td>59.6 ± 15†</td>
<td>61.6 ± 16</td>
</tr>
<tr>
<td>&gt;65 years (%)</td>
<td>46.3</td>
<td>56.6</td>
<td>38.2</td>
<td>47.0</td>
</tr>
<tr>
<td>Months of patient observation (mean ± SD) [median]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-index</td>
<td>18.7 ± 10 [17.2]</td>
<td>17.7 ± 10 [16.3]</td>
<td>19.4 ± 10 [18.3]</td>
<td>18.6 ± 10 [17.1]</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bleed during 3 months pre-index</td>
<td>8.3%</td>
<td>9.1%</td>
<td>9.1%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Pre-index distinct medications (mean ± SD) [median]</td>
<td>7.4 ± 6</td>
<td>7.2 ± 5</td>
<td>7.2 ± 6</td>
<td>7.3 ± 6</td>
</tr>
<tr>
<td>Pre-index cost (mean ± SD) [median]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$1,111 ± $2847[273]</td>
<td>$973 ± $1,705[340]</td>
<td>$1,078 ± $2,213[197]</td>
<td>$1083 ± $2,606[276]</td>
</tr>
<tr>
<td>Index VTE length of stay (mean ± SD) [median]</td>
<td>5.3 ± 4.2 days</td>
<td>8.0 ± 5 days*</td>
<td>8.3 ± 3.8 days†‡</td>
<td>6.1 ± 4.5 days*</td>
</tr>
<tr>
<td>Post-index treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin monotherapy</td>
<td>1,212 (80.9%)</td>
<td>339 (90.9%)</td>
<td>235 (85.3%)</td>
<td>1,786 (83.2%)</td>
</tr>
<tr>
<td>LMWH and warfarin</td>
<td>222 (14.8%)</td>
<td>30 (8.0%)</td>
<td>31 (11.3%)</td>
<td>283 (13.2%)</td>
</tr>
<tr>
<td>LMWH and UFH and warfarin</td>
<td>16 (1.1%)</td>
<td>1 (0.3%)</td>
<td>4 (1.5%)</td>
<td>21 (1.0%)</td>
</tr>
<tr>
<td>LMWH monotherapy</td>
<td>39 (2.6%)</td>
<td>1 (0.3%)</td>
<td>4 (1.5%)</td>
<td>44 (2.0%)</td>
</tr>
<tr>
<td>LMWH and UFH (no warfarin)</td>
<td>10 (0.7%)</td>
<td>2 (0.5%)</td>
<td>1 (0.4%)</td>
<td>13 (0.6%)</td>
</tr>
<tr>
<td>Months of warfarin after initial VTE event (mean ± SD) [median]</td>
<td>6.2 ± 6</td>
<td>7.9 ± 6*</td>
<td>8.0 ± 6†‡</td>
<td>6.7 ± 6*</td>
</tr>
<tr>
<td>Days of outpatient LMWH therapy after initial VTE event (mean ± SD) [median]</td>
<td>13 ± 21</td>
<td>20 ± 33</td>
<td>14 ± 30</td>
<td>14 ± 23</td>
</tr>
<tr>
<td>INR utilization (mean ± SD) [median]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR utilization rate¶</td>
<td>1.86</td>
<td>1.87</td>
<td>1.87</td>
<td>1.86</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[1.84 - 1.90]</td>
<td>[1.81 - 1.91]</td>
<td>[1.82 - 1.94]</td>
<td>[1.84 - 1.89]</td>
</tr>
</tbody>
</table>

* Significance compared with DVT group at P < 0.05 level (PE vs. DVT).
† Significance compared with DVT group at P < 0.05 level (DVT + PE vs. DVT).
‡ Significance compared with PE group at P < 0.05 level (DVT + PE vs. PE).
§ Distinct chemical entities.
¶ Calculated for patients who received an outpatient course of LMWH.
CI = confidence interval; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism.

Data are presented as mean ± standard deviation [median] or column percentage. All costs were collected from the “amount paid” fields from the administrative claims databases. Pre-index costs include amount paid for all claims regardless of diagnosis (i.e., all-cause). Index event costs are amount paid for inpatient claims with the specific index diagnosis.
Longitudinal Evaluation of Health Plan Cost per Venous Thromboembolism or Bleed Event in Patients With a Prior Venous Thromboembolism Event During Hospitalization

Table 4 Risk Factors Stratified by Index VTE Diagnosis (N=2,147)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>DVT (%)</th>
<th>PE (%)</th>
<th>DVT + PE (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1,499</td>
<td>n=373</td>
<td>n=275</td>
<td>n=2,147</td>
</tr>
<tr>
<td>History of or active malignancy</td>
<td>59.8</td>
<td>56.8</td>
<td>59.3</td>
<td>59.2</td>
</tr>
<tr>
<td>Other cardiac diseases</td>
<td>53.4</td>
<td>59.8</td>
<td>58.9</td>
<td>55.2*</td>
</tr>
<tr>
<td>Coagulation defects</td>
<td>27.0</td>
<td>30.6</td>
<td>34.9</td>
<td>28.6*</td>
</tr>
<tr>
<td>Trauma</td>
<td>24.0</td>
<td>26.3</td>
<td>24.7</td>
<td>24.5</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21.0</td>
<td>28.7</td>
<td>25.5</td>
<td>22.9*</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>20.0</td>
<td>30.8</td>
<td>23.3</td>
<td>22.3*</td>
</tr>
<tr>
<td>Contraception or estrogen therapy use</td>
<td>22.2</td>
<td>20.9</td>
<td>21.1</td>
<td>21.8</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>20.4</td>
<td>24.1</td>
<td>17.1</td>
<td>20.6</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>12.8</td>
<td>10.2</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>12.3</td>
<td>9.65</td>
<td>8.73</td>
<td>11.4</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9.47</td>
<td>14.5</td>
<td>9.09</td>
<td>10.3*</td>
</tr>
<tr>
<td>Surgery</td>
<td>7.27</td>
<td>5.36</td>
<td>5.82</td>
<td>6.75</td>
</tr>
<tr>
<td>Hyperviscosity syndromes</td>
<td>2.47</td>
<td>2.95</td>
<td>3.27</td>
<td>2.65</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1.47</td>
<td>1.07</td>
<td>1.09</td>
<td>1.35</td>
</tr>
</tbody>
</table>

Risk factors were assessed over entire observation period (both preindex and postindex).
*Pearson’s chi-square P value <0.05.
DVT = deep vein thrombosis; PE = pulmonary embolism.

Diagnosis of DVT + PE. A total of 994 (46.3%) patients were male, and 1,009 (47.0%) were aged 65 years or older. The average duration of the preindex and postindex period was 18.6 ± 10.0 (median, 17.1) and 21.3 ± 10.0 (median, 19.2) months, respectively. Patients received a mean of 7.3 ± 6.0 distinct medications (of all types) during the preindex period. The history of any bleed (i.e., from the list in Table 1) in the 3 months preceding the index VTE ranged from 8.3% to 9.0%, and the incidence was not significantly different among the 3 index diagnosis groups (ANOVA F = 0.2; P = 0.81). Preindex medical, pharmacy, and total health care costs were similar among the 3 index diagnosis groups by ANOVA (F < 0.42; P > 0.65 for all comparisons).

Table 4 provides a list of risk factors stratified by index diagnosis. Patients with an active case or history of malignancy and/or cardiac diseases (excluding atrial fibrillation, congestive heart failure, and myocardial infarction) had the highest representation in the cohort.

Follow-up Events and Costs

Table 5 illustrates the number of patients during the follow-up period who had at least 1 VTE event, the number of total events observed, and the associated total cost. Overall, 534 patients (24.9% of the original 2,147) experienced 662 VTE and bleed events requiring hospitalization during the follow-up period.

A total of 288 patients experienced 361 recurrent VTE events, 169 patients experienced 211 bleed events, and 77 patients experienced 90 combined VTE + bleed events during the follow-up period. The health system incurred a weighted average of $14,975 in extra cost per VTE event due to the occurrence of postindex events that required hospitalization. Weights were calculated based on the number of events in each event group. This translates into an additional annualized cost to the plan of $2,101 per patient per year (PPPY) diagnosed with an incident VTE ($14,975 × [534/2,147 patients] × [12 months/21.3 months]). We found that 612 (28.5%) patients suffered 1,489 bleed events that did not require hospitalization. Notably, 1,146 patients (612 + 534 = 1,146) or 53.4% experienced at least 1 event in the postindex period.

Unadjusted and multivariate modeling for all pair-wise comparisons between groups yielded no significant differences in costs for all types of follow-up events requiring hospitalization. Of note, the costs to treat recurrent VTE requiring hospitalization between the PE and the DVT + PE groups did not reach statistical significance (P=0.11). Although the observed difference in costs for bleeds not requiring hospitalization between the PE and DVT + PE groups was small, this difference did reach statistical significance in the multivariate model (Wald P <0.05).

In all multivariate models, cardiac events, malignancy, trauma, and surgery were significantly associated with increased cost. In addition, the INR monitoring rate was not a significant term (Wald P >0.15) in any of the 4 models.

Figure 1 shows the component costs for each derived resource center by each of the 3 types of recurrent events requiring hospitalization. The percentages of total costs were consistent between groups, with room and board costs accounting for the highest percentage of total costs.

Index Thrombosis Event

The index VTE length of stay (LOS) was 5.3 ± 4.2 (median, 5) days for the DVT group; 8.0 ± 5.0 (median, 7.0) days for the PE group; and 8.3 ± 3.8 (median, 8) days for the DVT + PE group. Of note, 17% of patients had an LOS of ≤ 1 day. The DVT group LOS was significantly shorter than both the PE and DVT + PE groups (P <0.05). It was observed that 211 (9.8%) patients were transferred directly from the hospital to an SNF. The overall LOS for this group was 53 ± 55 days (median, 32), and all pair-wise comparisons between index VTE groups were not significantly different.

The overall cost for the index VTE event, including any contiguous skilled facility care, was $8,331 ± $18,667 (median, $4,003). By diagnosis group, cost for the index VTE event was $7,712 ± $18,339 (median, $3,131) for DVT; $9,566 ± $13,512 (median, $6,424) for PE; and $12,200 ± $24,038 (median, $6,678) for DVT + PE. Both the PE and DVT + PE groups had significantly higher costs compared with the DVT group (P <0.05). These costs by resource center were 3.7% from the emergency department, 53.0% from room and board, 9.7% from both diagnostic/laboratory and pharmacy, and 23.8% from...
Longitudinal Evaluation of Health Plan Cost per Venous Thromboembolism or Bleed Event in Patients With a Prior Venous Thromboembolism Event During Hospitalization

### Anticoagulation Therapy and Monitoring Secondary Outcomes

A total of 2,090 patients received warfarin therapy after the index VTE event, 283 (13.2% of 2,147 study patients) in combination with LMWH. Average therapy time for the DVT group was 6.2 ± 6.0 (median, 4.4) months; for the PE group, 7.9 ± 6.0 (median 6.3) months; and for the DVT + PE group, 8.0 ± 7.0 (median, 6.2) months. Duration of therapy was significantly longer in both the PE and the DVT + PE groups compared with the DVT group (P <0.05). Overall, the average warfarin cost was $130 ± $174 (median, $72), or $19.40 per utilizing patient per month (PPPM). Of note, 361 patients received an outpatient course of LMWH therapy, with a duration and cost of 14.2 ± 23.0 days (median, 7); and $703 ± $1,540 (median, $316; $50 per patient-day), respectively. No difference was observed between groups with respect to the duration or cost of LMWH therapy.

For patients receiving warfarin, a patient received a mean of 13.5 ± 13.0 (median, 10) PT/INR tests or 1.86 tests PPPM over the course of warfarin therapy. PT/INR test rates were nearly identical for all index diagnosis groups. The average cost for PT/INR testing was $84 ± $220 (median, $42), or $12.50 PPPM. Additionally, 611 (29.2%) patients had at least 1 office visit within a day of the PT/INR laboratory performance; the cost for these office visits potentially attributable to warfarin monitoring was $127 ± 162 (median, $79), or $18.96 PPPM.

### Discussion

In this analysis, we conducted a retrospective cohort study of patients gathered from 2 large U.S. managed care populations with the primary objective of determining the cost and utilization of medical resources associated with managing VTE follow-up events. This population was identified by the occurrence of an index VTE hospital event and was at high risk for VTE (e.g., 59% overall with history of malignancy or active malignancy), allowing observation of customary management of VTE outside of a controlled clinical trial. Of the 2,147 patients identified with an incident VTE hospital event, 534 patients (24.9%) experienced at least 1 bleed event during the follow-up period that did not require hospitalization.

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### Table 5: Postindex VTE/Bleed Events and Mean Total Costs per Event by Index Diagnosis Group

<table>
<thead>
<tr>
<th>Recurrent Events Requiring Hospitalization</th>
<th>DVT n = 1,499</th>
<th>PE n = 373</th>
<th>DVT + PE n = 275</th>
<th>Overall n = 2,147</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>221</td>
<td>221</td>
<td>371</td>
<td>613</td>
</tr>
<tr>
<td>No. of events per patient</td>
<td>1.21</td>
<td>1.30</td>
<td>1.35</td>
<td>1.50</td>
</tr>
<tr>
<td><strong>Bleed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>145</td>
<td>43</td>
<td>23</td>
<td>211</td>
</tr>
<tr>
<td>No. of events per patient</td>
<td>1.25</td>
<td>1.23</td>
<td>1.28</td>
<td>1.25</td>
</tr>
<tr>
<td><strong>VTE + bleed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>44 (2.9%)</td>
<td>23 (6.2%)</td>
<td>10 (3.6%)</td>
<td>77 (3.6%)</td>
</tr>
<tr>
<td>No. of events per patient</td>
<td>1.11</td>
<td>1.22</td>
<td>1.30</td>
<td>1.17</td>
</tr>
<tr>
<td>Weighted average†</td>
<td>$13,920</td>
<td>$16,947</td>
<td>$16,767</td>
<td>$14,975</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent Events Not Requiring Hospitalization</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>1,022</td>
<td>275</td>
<td>294</td>
<td>1,591</td>
</tr>
<tr>
<td>No. of events per patient</td>
<td>2.47</td>
<td>2.39</td>
<td>2.29</td>
<td>2.43</td>
</tr>
<tr>
<td>Total cost (mean ± SD) [median]</td>
<td>$235 ± $367 [95]</td>
<td>$266 ± $387 [114]</td>
<td>$222 ± $470 [70]</td>
<td>$239 ± $386 [95]</td>
</tr>
</tbody>
</table>

* Cost are presented for patients having at least 1 event during follow-up, costs are reported per event and obtained from the “amount paid” field in administrative claims.
† Frequency weighted based on number of patients having at least 1 recurrent event.
‡ Wald P value <0.05 as compared with DVT; all other pair-wise comparisons were not different.

DVT = deep vein thrombosis; N = patients having at least 1 event; PE = pulmonary embolism; VTE = venous thromboembolism.
Previous observational studies that were either economically based or formed a component of a clinical trial directly compared the savings or cost-effectiveness of LMWH with UFH. These studies focused on a wide variety of settings and management strategies, such as prospective outpatient management of recurrent thromboembolism events (100, 125, and 107 patients)\cite{20-31}; randomized, multicenter trials\cite{32-33}; decision modeling approaches\cite{34}, and home-oriented pharmacy management.\cite{35} Two observational studies focused on detailing DVT costs of care from the MCO perspective over the first 90 days: (1) a prospective study inside a group-model HMO\cite{36} and (2) a retrospective study conducted in a staff-model HMO.\cite{37}

Spyropoulos et al., in a retrospective staff-model HMO study, followed 129 patients with DVT and reported an average cost of care for the first 90 days of between $9,347 and $11,930, depending on whether the initial treatment consisted of LMWH or UFH. The event rate over the follow-up period was found to be similar among groups, although much lower than in our analysis. The average initial hospitalization cost was between $4,849 and $8,501, a finding similar to our study.\cite{38}

Tillman et al. followed 391 patients with DVT in a group-model HMO, all acutely treated with LMWH, and reported an estimated cost of $4,695 per initial hospitalization.\cite{39}

One retrospective observational study conducted in a real-world setting detailed the cost of VTE care by using discharge data from 6 states.\cite{40} The study had a payer mix of 56.0% Medicare, 22.5% managed care, and 21.5% not reported. The average cost of initial hospitalization was $5,779, $9,476, and $11,189 for DVT, DVT + PE, and DVT with major bleed, respectively. Report on follow-up, from only 1 of the original 6 states, noted a 9.5% 6-month DVT recurrence rate with an average cost of $6,946.

Our study built on this previous research by including a larger sample size, a longer duration of follow-up, actual costs for all types of resources, and data from 2 geographically disparate MCOs. We also placed more emphasis on detailing and comparing cost drivers and costs to treat recurrent events on a per-event basis.

In addition, our data complement Anderson's recent cost analysis of pharmacist-driven, outpatient anticoagulation services for atrial fibrillation patients on chronic warfarin therapy.\cite{41} First, he found that anticoagulation medication costs were $19.09 PPPM, nearly identical to the $19.40 PPPM result reported in our study. Second, our data provide the means to perform the cost-avoidance analysis that Anderson suggested be performed to determine the true cost impact of an outpatient oral anticoagulant monitoring service since we provide the cost of events that occur despite anticoagulant therapy. Future research might include a cost-avoidance/impact analysis comparing current anticoagulant strategies with newer therapies with different acquisition costs and effectiveness/risk parameters.
Limitations
Several limitations to the present study should be noted. First, due to the retrospective design of our study, only associations can be calculated between the variables of interest and the outcomes (i.e., it is not possible to speculate about causality).

Second, although multivariate techniques were used, administrative claims data do not account for all potential confounders. Although these techniques are well accepted in determining adjusted estimates, they cannot adjust for all differences present in the case mix because certain variables (e.g., race, socioeconomic status, hospital type) are not available.

Third, coding errors have been well documented in administrative claims data. Up-coding, the existence of a VTE or bleed code as part of a rule-out admission, may have existed during the follow-up period in our study. Additionally, patients with a VTE prior to the preindex period could be included in this study, which would tend to select higher-risk patients compared with a longer preindex period (i.e., a patient with a history of VTE events would be more likely to be admitted to our study). Other studies attempting to measure such events have observed a recurrent VTE rate of 5.1% to 8.6%, and a bleed rate requiring admission of 2.6% and 2.7%, respectively. However, none of these studies observed patients outside the constructs of a clinical trial, highly specialized clinic, or other tertiary centers of care; thus, it is plausible for our rates of recurrent VTE and bleed to be higher. In addition, although this rate of up-coding is not known, this postulated vigilance toward rule-out admissions does represent a cost to the system and should be factored into the mean costs. Also, the effect of including up-coding in the analysis would be expected to decrease the mean cost per event.

Fourth, there were 77 patients with a recurrent VTE and bleed event requiring hospitalization. It would be prudent to assume that a proportion of these events represented a bleed event alone rather than a recurrent VTE and a subsequent inpatient bleed. However, it should be noted that the average cost per VTE and bleed was approximately 57% and 97% higher than just a bleed or VTE, respectively. This trend in mean costs suggests that a higher volume of care may have been provided to patients with VTE and bleed. Future research should be undertaken to combine hospital chart-level data with administrative claims data to assist in verifying VTE diagnoses and provide greater depth and granularity of data from the inpatient setting.

Fifth, we only studied the costs associated with adverse events and INR monitoring. Potential new therapies may be associated with other adverse outcomes or may require laboratory monitoring other than INR.

Sixth, this evaluation did not include an examination of the effect of pharmacy benefit design and coverage on clinical or economic outcome. Nearly one half (47%) of the study population was older than 65 years. We did not measure the proportion of this population who were members of a Medicare HMO with a pharmacy benefit that included biannual or annual benefit dollar maximums; the drug benefit annual maximums varied based on the county of residence. Out-of-pocket cost may have been a factor in adherence to drug therapy including warfarin, although the average wholesale cost of warfarin was only about $30 per month of therapy at the time of this study. Nevertheless, additional analysis of these patients, their specific pharmacy benefit design, and their adherence to warfarin therapy may provide insight regarding the impact of benefit design on health outcomes in this age group.

Seventh, administrative claims capture neither mortality nor the clinical data necessary to permit classification of major and minor bleeds. Hence, we used hospitalized/not hospitalized as a proxy for bleed severity to describe the events since these were measures we could retrieve from an administrative claims database. Due to the absence in medical claims of specific J-codes available at the time of this study, LMWH was captured in the outpatient setting only from pharmacy claims, which would tend to leave the true cost of LMWH therapy in this patient population underreported.

Eighth, we did not have the ability to assess the effects of an anticoagulation management clinic on the incidence of rehospitalization and associated expenses. The presence of an anticoagulation clinic would be expected to decrease the adverse events that precipitated repeat hospitalizations.

Finally, a total of 100 patients (4.7%) had ICD-9 codes that could have been for heparin-induced thrombocytopenia (HIT); 67 patients (3.1%), unspecified thrombocytopenia (codes 287.5); 21 patients (0.98%), secondary thrombocytopenia (drug-induced, code 287.4); and 6 patients (28.0%) had codes for both. These results are in agreement with estimates for the prevalence of HIT from 0.2% to 5%. Costs for HIT patients were not specifically captured and are included in the total costs.

Conclusions
We observed costs attributable to VTE care in a longitudinal analysis from a managed care payer perspective. We focused on the cost per event so that managed care decision makers can better evaluate local health plan formularies for existing and new medication therapies and programs such as anticoagulation clinics. Since bleed and recurrent VTE events that require rehospitalization may occur in approximately 25% of patients presenting with an initial VTE event and cost the health plan approximately $15,000 per event, management strategies and therapeutic options are worthwhile considerations for MCOs.

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DISCLOSURES

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REFERENCES


28. STATA Corporation LP. College Station, TX, 2004.


Utilization and Cost of Sildenafil in a Large Managed Care Organization With a Quantity Limit on Sildenafil

CATHERINE E. COOKE, PharmD, BCPS; WINSTON WONG, PharmD, MBA; and HELEN LEE, PharmD, MBA

ABSTRACT

OBJECTIVE: Erectile dysfunction (ED) affects approximately 30 million men in the United States. The objectives of this study were to (1) assess the cost and utilization of sildenafil citrate (Viagra), an oral therapeutic agent for ED, in a large managed care organization (MCO) with a quantity limit of 6 units per 30-day supply and (2) describe the incidence of comorbid conditions and the severity of cardiovascular disease in adult male users of sildenafil.

METHODS: Pharmacy claims for sildenafil were identified from an administrative database of claims with dates of service in calendar year 2001 for male members aged 18 years or older. Medical claims for MCO members who had sildenafil claims were used to identify comorbid diseases and categorize patients by age and medication history.

RESULTS: There were 67,914 pharmacy claims for sildenafil during 2001 for 20,281 MCO members, an average of 3.3 pharmacy claims per patient. The prevalence of sildenafil use was 54.1 per 1,000 male MCO members aged 18 years or older. The total allowed charges for sildenafil pharmacy claims in 2001 were $3.56 million, of which patients paid 26.6% in average cost-share, and the net MCO cost per member per month (PMPM) was $0.18. A total of 1,681 patients (81.0%) paid cash and 319 (19.0%, or 1.6% of all sildenafil users) appealed the MCO's denial of additional sildenafil tablets beyond the restriction of 6 tablets per month. Medical claims were available for 15,644 sildenafil users (77.1%), and 12,720 sildenafil users (81.3% of those with medical claims) were judged to be at high or medium cardiovascular risk.

CONCLUSIONS: A quantity limit of 6 tablets of sildenafil per 30-day period was associated with a drug cost to users and the MCO of $0.25 PMPM. Sildenafil users paid an average cost-share of 26.6%, resulting in a net drug cost of $0.18 PMPM to the MCO.

KEYWORDS: Erectile dysfunction, Sildenafil citrate, Viagra, Quantity restriction, PMPM cost

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Erectile Dysfunction: Treatment, Costs, and Interventions. Treatment of Erectile Dysfunction

Erectile dysfunction can be characterized as organic, psychogenic, or mixed in origin, with treatment ranging from psychological to medical to hormonal, or a combination of these. The American Association of Clinical Endocrinologists (AACE) recommends trying to identify the cause of sexual dysfunction first, with a thorough evaluation that should include some or all of the following: medical evaluation, blood tests, vascular assessment, sensory studies, and nocturnal penile tumescence and rigidity testing. When the cause of ED is organic, the AACE recommends identifying the medical risk factors and correcting them. For example, determining whether medications for other comorbid conditions may be the source of or a contributing factor to the patient's ED is a primary step.

The first oral medical treatment for ED, sildenafil citrate (Viagra), was approved by the U.S. Food and Drug Administration on March 27, 1998. Sildenafil selectively inhibits phosphodiesterase type 5, which is found in vascular smooth
muscle throughout the body but in much higher concentrations in the vascular smooth muscle of the penis. Sildenafil has been shown in clinical trials to be an effective and well-tolerated treatment in patients with ED, including patients with comorbid medical conditions. In a meta-analysis of 27 trials involving 6,659 men, Fink et al. found that sildenafil improves erectile function and is well tolerated by men of varying health status. In a double-blind, placebo-controlled study of sildenafil in men with ED and clinically stable coronary artery disease, DeBusk et al. reported that more patients taking sildenafil had improved erections (64% versus 21%) and improved intercourse (65% versus 19%) than those taking placebo, with no serious drug-related cardiovascular consequences. In a retrospective analysis of data from multiple efficacy and safety studies of sildenafil in patients with ED and ischemic heart disease who were not taking nitrates, Conti et al. reported improved erections in patients taking sildenafil compared with those taking placebo (70% versus 20%).

Costs and Economics of Sildenafil

The introduction of sildenafil for ED and the growing public awareness of ED resulted in an 84% increase in the number of U.S. men seeking and using treatments for ED from 1998 through 2002. Within 2 years of the introduction of sildenafil, the number of patient visits for the chief complaint of ED increased in Mexico (279%), the United States (250%), the United Kingdom (103%), Spain (90%), and Germany (55%). Wilson et al. attributed the rising cost of managing ED in the United Kingdom to a 3-fold increase in the number of men visiting their general practitioners for ED, many of whom are referred to specialists. Health plans have been concerned about the impact sildenafil will have on their pharmacy budgets because of the nature of the disease it treats, namely, that ED is a self-reported condition, and, for this reason, potentially large numbers of men could seek to obtain sildenafil for self-reported ED.

Several studies, however, have shown that sildenafil has not had the adverse economic effect initially anticipated. For example, Smith et al. found the cost-effectiveness of sildenafil treatment to be comparable to accepted therapies for other medical conditions, such as cholesterol-lowering medications, coronary artery bypass grafting, and renal dialysis. Smith et al. suggested that sildenafil is in the same category as other treatments for non–life-threatening illnesses that affect only quality of life and are covered by insurance, such as migraine headaches.

Although there are no articles published on evaluation of the costs associated with adding sildenafil coverage in a managed care drug benefit plan, 3 studies, in abstract form, found only lower than expected pharmacy benefit costs. Lehman and Duttagupta discovered that the drug costs per member per month (PMPM) of adding sildenafil coverage to 4 health plans with 93,000 to 15 million members ranged from $0.04 to $0.21, much less than the predicted estimate of $1.00. In a study evaluating PMPM drug costs of sildenafil in managed care organizations (MCOs) that did not restrict the quantity of tablets dispensed, Cherayil and Duttagupta found that actual PMPM costs ($0.03 to $0.24) were also significantly lower than the projections. When MCOs did impose restrictions on the number of sildenafil tablets allowed per prescription, but without requirement for prior authorization for sildenafil, drug costs were also lower than expected, at $0.07 to $0.18 PMPM.

Managed Care Interventions

Among the methods employed by MCOs to control pharmacy costs is exclusion from coverage, imposition of quantity limits, or higher copayments. In a study examining which factors MCOs use to make drug coverage decisions, Titlow et al. concluded that value judgments, rather than cost, seemed to play a central, though largely unspoken, role in drug coverage decisions. For sildenafil in particular, Titlow et al. discovered, among 53 organizations surveyed, that the most common method of controlling sildenafil cost was by limiting the quantity of medication covered or the duration of its use. Sixty-four percent of MCOs placed limits on sildenafil coverage, 23% did not cover treatment for sexual dysfunction at all, 21% required prior authorization, and only 2% of MCOs covered sildenafil without any restrictions. Other research has found the quantity limit for sildenafil to range from 4 to 12 tablets per month.

The present study analyzes sildenafil utilization and cost associated with a quantity limit of 6 units per 30-day supply and describes the incidence of comorbid conditions and the severity of cardiovascular disease in sildenafil users in a large MCO with 1.2 million pharmacy lives.

Methods

Pharmacy claims data for sildenafil for calendar year 2001 were obtained from the pharmacy benefit management company of a large MCO with 1.2 million pharmacy lives located in the mid-Atlantic states. Medicare beneficiaries, who comprised 2.5% of the MCO population, were eligible for a senior pharmacy benefit drug program, which had an annual benefit maximum of $1,000. At the time of this study, sildenafil was on the second tier of the drug formulary and was restricted to a maximum of 6 tablets per month (or up to 18 tablets for a 3-month supply). There was a gender edit that permitted only male members to receive sildenafil. The refill-too-soon edit was 75%, meaning that a covered member could not obtain a refill of sildenafil until at least 75% of the days in the period had transpired, 23 days for a 30-day pharmacy claim or 68 days for a 90-day pharmacy claim for sildenafil. Physicians could appeal sildenafil claim denials, and decisions were made on a case-by-case basis since there were no specific criteria for medical exception. The study cohort was composed of men aged 18 years or older with...
continuous pharmacy benefits for calendar year 2001 and with at least 1 pharmacy claim for sildenafil during the calendar year.

In the pharmacy claims database, there were both positive and negative (reversed) claims. Pharmacists generate a positive claim when tablets are dispensed by the pharmacy, and a negative claim occurs when the filled prescription is reversed. Reasons for negative claims include an error in the submission of the electronic claim or if the member does not pick up the prescription. All positive and negative matched claim pairs were deleted to ensure that only prescriptions received by members were included in the data used in this study.

The data set contained the following fields: unique generator member identification, which was different from the member’s actual identification to protect member confidentiality; age as of January 1, 2001; amount paid by the MCO; amount of member copayment; drug name; dispense date; dose; number of tablets dispensed; and the days supply (number of drug therapy days submitted by the pharmacist on the pharmacy claim).

Members who received sildenafil were grouped into high-, medium-, and low-cardiovascular-risk categories based on an adaptation of classification criteria in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline. The high-risk category consisted of patients with at least 1 of the following diagnoses: diabetes mellitus, ischemic heart disease, abdominal aortic aneurysm, or peripheral arterial disease. Patients in the medium-risk category were those who did not have any diagnoses from the high-risk category but had at least 1 of the following cardiovascular risk factors: smoking, hypertension, hypercholesterolemia, family history of premature coronary heart disease, or were aged 45 years or older. The remaining patients were placed into the low-risk category.

### Results

A total of 67,914 prescription claims for sildenafil occurring during calendar year 2001 for 20,281 patients were available for analysis. The prevalence of sildenafil use was 54.1 per 1,000 male MCO members aged 18 years or older. The mean ± standard deviation (SD) age of patients in the cohort was 53.1 ± 10.4 (median 53) years. Most of the patients in the cohort were between age 50 and 59 years (38.5%) (Table 1). There were 2,559 sildenafil patients (12.6%) enrolled in a senior pharmacy benefit program for Medicare beneficiaries with a $1,000 annual benefit maximum.

The number of sildenafil prescriptions filled per utilizing member for this MCO cohort during 2001 was 3.3 ± 2.7 (mean ± SD; median = 2), with a range of 1 to 29 prescriptions (Table 2). Most prescriptions (85%) were for 6 tablets at a time (6.3 ± 2.4; median = 6), with a range of 1 to 100 tablets. Some (9.3%) prescriptions were for fewer than 6 tablets, and some were for 7 or more tablets (3.4% for 7 to 11 tablets and 2.5% for 12 or more tablets).

Median annual sildenafil utilization for calendar year 2001, extrapolated from partial-year use, was 29.4 tablets per utilizing member per year, or 2.5 tablets per month, which includes both cash and MCO-paid pharmacy claims. There were 933 pharmacy claims (1.4%) for 6,127 tablets of the 25 mg dose of sildenafil, whereas the remainder of the prescriptions was evenly split between 33,208 pharmacy claims (207,994 tablets) for the 50 mg dose (48.9%) and 33,773 pharmacy claims (213,471 tablets) for the 100 mg dose (49.7%). A total of 1,681 members (8.3%) exceeded their quantity restrictions for sildenafil tablets in 2001, of which 1,362 (81.0%) paid cash for the additional tablets, and 319 (19.0%) appealed and received approval from the MCO for additional sildenafil tablets beyond the limit of 6 tablets per month. Total pharmacy benefit expenditures in 2001 were $516 million for this MCO with 1.2 million members or about $36 PMPM in MCO costs after subtraction of member cost-share but before the effect of manufacturer rebates. The MCO spent $2.6 million on sildenafil prescriptions in 2001, approximately $0.18 PMPM, or about 0.5% of the annual costs.
pharmacy budget. Costs for the MCO were divided nearly equally between the 50 mg ($1.2 million) and 100 mg ($1.3 million) doses of sildenafil, with the 25 mg dose accounting for $36,726 of the pharmacy budget in 2001.

The total allowed charges for sildenafil pharmacy claims in 2001 were $3.56 million, of which members paid 26.6% ($0.944 million) in average cost-share and the MCO net cost was $2.61 million. Members of the MCO had varying levels of copayments and total out-of-pocket costs for sildenafil. The average copayment per sildenafil pharmacy claim in 2001 was $13.90 ± $8.67 (mean ± SD; median = $15), with a range of $0 to $240. The average member copayment in 2001 for any sildenafil claim was $14.70 ± $8.82 (median = $15), with a range of $0 to $240. The total out-of-pocket cost for sildenafil per member for the year was $46.55 ± $45.01 (median = $30), with a range of $0 to $623.

More than half of the 18,899 members had their first sildenafil prescription for the year filled in the first quarter of 2001 (9,722 members, 51.4%). Successively lower numbers of members filled their first prescription in the second (3,620 members, 19.1%), third (2,925 members, 15.5%), and fourth quarters (2,632 members, 13.9%), respectively.

Medical Claims Data and Member Comorbidity
Among the 20,281 patients who had sildenafil claims in 2001, there were 15,644 patients (77.1%) who had at least 1 medical claim for a comorbid disorder. The mean ± SD age of members in this group was 53.4 ± 9.9 (median 54) years. A total of 135,298 medical claims (average 8.65 per patient) were included in the evaluation. About 81% of these sildenafil users were classified as either high risk or medium risk for cardiovascular events based on an adaptation of the risk factor classification outlined by the NCEP ATP III guideline.28 Hypertension (37%), dyslipidemia (36%), and diabetes mellitus (18%) were the most common comorbid conditions. (Table 3)

Discussion
Our study found that most (85%) members from the MCO filling sildenafil prescriptions were between the ages of 40 and 69 years, with 10% of members younger than 40 years and 5% of members 70 years or older. These results are consistent with other published research describing the characteristics of sildenafil users.29

In a study evaluating sildenafil prescribing practices immediately after its approval, Harrold et al. found that patients prescribed sildenafil tended to remain on the initial dose they were prescribed, with little reported dose titration.29 The majority (59%) of patients were initially prescribed the 50 mg dose, with 35% prescribed an initial dose of 25 mg and 7% prescribed an initial dose of 100 mg. In the present study, only 1.4% of pharmacy claims were for the 25 mg dose of sildenafil, and about one half (48.9%) of all sildenafil pharmacy claims were for the 50 mg dose and one half (49.7%) were for the 100 mg dose.

Our median annual sildenafil utilization for calendar year 2001 was 29.4 tablets per year, or 2.5 tablets per month, which corresponds to results from a study by Delate et al.,17 who found that the mean tablets dispensed over a 9-month period ranged from 21.0 to 23.5 (2.3 to 2.6 tablets per month) over the 5 years of pharmacy claims included in their analysis. For their study year 2001, corresponding to the data from our cohort, the mean

| Table 2 Frequency Distribution of Sildenafil Claims Among Users in 2001 |
|----------------|-----------------|----------------|
| No. of Claims | No. of Patients | % of Total |
| 1             | 6,925           | 34.1         |
| 2             | 3,693           | 18.2         |
| 3             | 2,465           | 12.2         |
| 4             | 1,805           | 8.9          |
| 5             | 1,373           | 6.8          |
| 6             | 1,065           | 5.3          |
| 7+            | 2,955           | 14.6         |
| **Total**     | **20,281**      | **100.1**    |

* Total is greater than 100 due to rounding.

| Table 3 Cardiovascular Risk and Comorbid Conditions in Patients With Sildenafil Utilization |
|-----------------------------------------------|----------------|--------------|
| Cardiovascular Risk* | No. of Patients | %       |
| High risk            | 4,186            | 26.8       |
| Medium risk          | 8,534            | 54.6       |
| Low risk             | 2,924            | 18.7       |
| **Total**            | **15,644**       | **100**    |

<table>
<thead>
<tr>
<th>Comorbid Conditions‡</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>5,777</td>
<td>37</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5,570</td>
<td>36</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2,784</td>
<td>18</td>
</tr>
<tr>
<td>Hypertrophy of prostate</td>
<td>2,589</td>
<td>17</td>
</tr>
<tr>
<td>Chest pain, unspecified</td>
<td>2,057</td>
<td>13</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1,656</td>
<td>11</td>
</tr>
</tbody>
</table>

* High risk was defined as having at least 1 of the following diagnoses: diabetes mellitus, ischemic heart disease, abdominal aortic aneurysm, or peripheral arterial disease.

Medium risk was defined as not having any diagnosis in the high-risk category and at least 1 of the following cardiovascular risk factors: smoking, hypertension, hypercholesterolemia, family history of premature coronary heart disease, or being age 45 years or older.

Low risk was defined as all “other.”

‡ Medical claims were available for 15,644 (77.1%) of sildenafil users.

* A given sildenafil user may have more than 1 comorbid condition.
Utilization and Cost of Sildenafil in a Large Managed Care Organization With a Quantity Limit on Sildenafil

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A total of 8.3% of members exceeded their quantity restrictions for sildenafil tablets in 2001; 6.7% paid cash for the additional tablets, whereas 1.6% appealed and received approval for additional tablets from the MCO beyond the restriction of 6 tablets per month. Quantity restrictions did not appear to negatively impact most members because they did not maximize their benefit of 6 tablets per month. Previous research found that just over 50% of patients who use sildenafil for the first time respond on the first attempt at sexual intercourse, but at least 6 attempts are required before an 80% success rate is achieved.30,31 Educating patients regarding expectations and the possibility of increasing the dose is important to treatment success. Atieno et al. found that 42% of prior sildenafil non-responders achieved success after reeducation, with 81% of the failures being attributed to incorrect administration.32 About 94% of the patients had a sustained response at 26 months.

We were able to determine comorbidity occurrence for members using sildenafil who had medical coverage and at least 1 medical claim. We found hypertension, dyslipidemia, and diabetes mellitus to be the top 3 comorbid diagnoses in men prescribed sildenafil. The results from the present study are consistent with other published research describing the characteristics of sildenafil users. Harrold et al. found that 49% of plan members from a Massachusetts health maintenance organization who received sildenafil also had hypertension, 42% had hyperlipidemia, 33% were receiving a medication associated with ED as a possible side effect (such as beta-blockers, diuretics, digoxin, antipsychotic agents, and others), 25% had diabetes mellitus, 16% had ischemic heart disease, and 5% had a history of radical prostatectomy.29 In the present study, 81% of members in whom comorbid health conditions could be determined, were classified as either high risk or medium risk for cardiovascular conditions. Previous studies have shown a strong link between ED and many of the conditions for which members in our cohort accessed medical care.3,4,6,26 In fact, Johannes et al. observed that the age-adjusted risk for ED was higher for men with diabetes, heart disease, and hypertension,4 which supports our data obtained from the medical claims.

Limitations

The data from the pharmacy benefit manager did not provide an indication or diagnosis for the use of sildenafil, which could affect interpretation of utilization patterns, such as the off-label use of sildenafil for primary pulmonary hypertension,33 and we did not assess the medical claims to determine diagnosis information for this purpose. Second, as with any analysis of pharmacy claims data, there was no way to determine whether the patient used the medication, only that the prescription was filled and the tablets were received by the patient.

Third, we could not determine from the database if cash payment for sildenafil prescriptions was due to exhaustion of benefits for those Medicare beneficiaries with an annual benefit maximum or by sildenafil users in excess of the quantity limit of 6 tablets per month. Of the 1,362 patients who paid cash for sildenafil, 136 (10.0%) were patients aged 65 years or older. We estimated but could not verify that 53 of these seniors exceeded their $1,000 annual benefit maximum, accounting for 3.9% of the patients who paid cash for sildenafil prescriptions. Conversely, approximately 96% of the cash prescriptions for sildenafil were assumed to be from patients who had exceeded the limit of 6 tablets per 30-day period.

We also could not determine how often members simply purchased sildenafil prescriptions outside of the pharmacy claims system due to the use of sildenafil in excess of the quantity limit. Our data may further underestimate the actual use of sildenafil because we could not account for samples provided by physicians to patients during medical encounters.

Because the data collection period was limited to 2001, it was not possible to determine duration of sildenafil use or to categorize patients as new or established sildenafil users. Drug use patterns may differ between new and established sildenafil users, and sildenafil had been available for about 3 years at the time of the study. The population for this MCO probably included both members initiating and continuing therapy with sildenafil, as might be expected for other MCO populations.

Our attempt to determine comorbid conditions in the study population was limited since medical claims were not found in 2001 for all sildenafil users; for example, a sildenafil user could have had a medical encounter prior to the 2001 study period. The medical record information was also limited by the maximum of 3 diagnosis codes per medical claim and may therefore be

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tablets dispensed over 9 months were 23.3 ± 20.5, which corresponds to approximately 2.6 tablets per month. Sildenafil accounted for about 0.5% of the annual pharmacy budget, with an MCO drug cost of $0.18 PMPM in 2001. This $0.18 PMPM drug cost for sildenafil falls in the range of the 3 poster abstracts reported previously ($0.03-$0.24 PMPM).23-25

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Scope of drug coverage and the amount of member cost-share are important factors in member satisfaction with the pharmacy benefit plan. Matheral and Heinle concluded that about 75% of respondents felt that their out-of-pocket copayment was the most important feature of their prescription benefit plan, with an additional 20% of respondents listing copayment as the second most important factor.31 Other factors considered included the list of drugs covered by the plan, having a mail-order option, which pharmacies accepted the plan, and getting help with questions or problems with drug coverage. In a survey evaluating member satisfaction with their pharmacy benefit plans, Desselle found that total out-of-pocket cost was the second most important factor out of 9 total factors rated by respondents.34 The only factor that ranked higher for plan satisfaction was the list of drugs on the formulary. The amount of medication (days supply) the plan allows for each pharmacy visit was ranked the third most important factor.

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incomplete. Other reasons for inaccurate or incomplete coding were possible, including accidental or intentional miscoding.

Lastly, at the time of our study, sildenafil was the only phosphodiesterase type 5 inhibitor on the market, and it may not be reasonable to extrapolate our findings to the current environment in which other ED therapies are now available. A recent clinical monograph on ED therapies was published in the Journal of Managed Care Pharmacy.36

Conclusions

Our study found that the majority of members who used sildenafil were between the ages of 40 and 69 years and had a medium to high risk for a cardiovascular event based on an adaptation of the classification system in the NCEP ATP III guideline for treatment of dyslipidemia. A quantity limit of 6 tablets of sildenafil per 30-day period was associated with a drug cost to users and the MCO of $0.25 PMPM. Sildenafil users paid an average cost-share of 26.6%, resulting in a net drug cost of $0.18 PMPM to the MCO. The impact of sildenafil on the MCO’s pharmacy budget was 0.5%, and 91.7% of members did not exceed their sildenafil quantity restriction.

DISCLOSURES

The authors disclose that no outside funding supported this study. Author Catherine E. Cooke is employed by Pfizer Inc., the manufacturer of sildenafil. Author Winston Wong discloses that he has received honoraria from and served on the advisory board of Pfizer Inc.; author Helen Lee discloses no potential bias or conflict of interest relating to this article. Cooke served as principal author of the study. Study concept and design were contributed primarily by Cooke and Wong. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was primarily the work of Cooke and Lee, and its critical revision was the work of all authors. Statistical expertise was contributed by Cooke.

REFERENCES


Clinical and Economic Outcomes of Conversion of Simvastatin to Lovastatin in a Group-Model Health Maintenance Organization

SARAH J. BILLUPS, PharmD, BCPs; SUSYN L. PLUSHNER, PharmD, BCPs; KARI L. OLSON, PharmD, BCPs; THOMAS J. KOEHLER, RPh, BCPs; and JANE KERZEE, PharmD, BCPs

ABSTRACT

OBJECTIVE: To (a) determine if converting patients on simvastatin to lovastatin affects whether they meet their low-density lipoprotein cholesterol (LDL-C) goals as defined by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) clinical practice guidelines and (b) assess the change in health care expenditures associated with such a conversion.

METHODS: Primary and secondary prevention patients receiving simvastatin 10 mg to 40 mg daily between September 1, 2001, and February 28, 2002, were offered lovastatin at a therapeutically equivalent dose. Fasting lipid profiles and alanine aminotransferase (ALT) levels were measured and recorded at least 6 weeks after starting lovastatin. A clinical pharmacy staff member, in collaboration with the subject’s primary care provider, subsequently adjusted lipid-lowering therapy as needed to attain target LDL-C goals, as determined by the ATP III clinical practice guidelines.

RESULTS: Of 5,286 patients converted to lovastatin and for whom follow-up laboratory tests were drawn, 5,046 (95.5%) were converted successfully, and 240 (4.5%) had to be converted back to simvastatin due to intolerance (N = 164, 3.1%) or failure to achieve LDL-C goal (N = 76, 1.4%). The proportion of patients with LDL-C at or less than their target goal increased from 75.9% before the intervention to 79.1% after conversion to lovastatin (P < 0.001). ALT levels did not change significantly. The mean ALT value, a proxy measure of safety before and after conversion for all patients, was 26.9 IU/L and 26.4 IU/L, respectively (P = 0.134). For the 2,235 patients converted from lovastatin 80 mg to simvastatin 40 mg, the mean pre-ALT and post-ALT values were 26.9 IU/L and 26.5 IU/L (P = 0.498). The annualized cost savings due to the conversions, expressed across the entire membership of this health maintenance organization (HMO), was $4.14 per member per year (PMPY), with no change in ALT levels. Patient savings in reduced copayments in the conversion from brand simvastatin to generic lovastatin were an average of $145.29 (62%) per patient (95% confidence interval, $143-$149,

CONCLUSION: A clinical pharmacy-directed program designed to convert patients from simvastatin to lovastatin resulted in substantial expenditure reductions for the HMO and 62% copayment savings for members, without compromise in clinical outcomes as measured by lipid control (effectiveness) and ALT levels (safety). The proportion of patients at or less than their LDL-C goal increased coincident with the conversion from simvastatin to lovastatin.

KEYWORDS: Lovastatin, Simvastatin, Cost-minimization analysis, Clinical pharmacist, Therapeutic conversion

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Dyslipidemia is highly prevalent in the United States. As of 2002, nearly 107 million Americans over 20 years of age had blood cholesterol levels greater than 200 mg/dL.1 When drug therapy is indicated, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are typically used as first-line therapy.2 Statin expenditures approached $12.5 billion in the United States in 2002. These expenditures will likely continue to increase as recommendations for initiating treatment expand to populations at high risk for cardiovascular disease (CVD), such as those with diabetes, peripheral arterial disease, and thromboembolic disease, and lipid goals become more aggressive.3,4

Currently, there are 6 statins on the market in the United States, which differ somewhat in their lipid-lowering potency.5 Of these, simvastatin, lovastatin, pravastatin, and atorvastatin have been evaluated in large clinical trials in patients with and without CVD and in patients with varying baseline cholesterol levels, and these trials have demonstrated reductions in morbidity and/or mortality.6,7-14 Although the potency of these agents varies on a mg-per-mg basis, comparative studies have shown that their lipid-lowering effects are similar when given in equipotent doses.6,15,16 A recent cohort study comparing clinical outcomes of patients using 1 of 5 different statins for secondary prevention found the statins to be equally effective at preventing acute myocardial infarction and death.17 When efficacy is comparable, providers may consider cost when deciding which statin to offer as a covered benefit.

Kaiser Permanente of Colorado (KPCO) includes both simvastatin and lovastatin on its drug formulary since both have demonstrated lipid-lowering capability and clinical benefit.10,12 Prior to January 2001, there was no preference for initiating statin therapy with either lovastatin or simvastatin. After January 2001, lovastatin became the only statin available on the U.S. market as a generic drug. As a result, the acquisition cost for group purchasing organizations was reduced, and lovastatin became the preferred drug of the statins.

Since the available evidence suggests that lovastatin can achieve similar low-density lipoprotein cholesterol (LDL-C) reduction compared with simvastatin when given in equipotent doses,6,15,16 this population-based study was conducted at KPCO among eligible patients with dyslipidemia to convert them from simvastatin to lovastatin in a safe, efficient manner, while maintaining lipid control. The purpose of this study was to evaluate both lipid and economic outcomes of this pharmacy-directed statin conversion project. Although medication conversions are not uncommon in health care settings, the large scale and
unique systems employed in this drug conversion differentiate this project from others. To assess the tolerability and efficacy of lovastatin 80 mg daily versus simvastatin 40 mg daily, we performed a subanalysis to supplement the limited data available for this lovastatin dose.17

Methods

Setting

This retrospective study was conducted at KPCO, a group-model health maintenance organization (HMO) providing medical care to members at 16 medical facilities throughout the Denver/Boulder metropolitan area. Each facility is staffed by 1 to 3 primary care clinical pharmacy staff (PCCPS) members who collaborate with primary care providers to facilitate clinically appropriate, cost-effective use of medications and to care for patients with drug-related problems. KPCO patients with CVD, defined as the presence of acute myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention with or without stent placement, or unstable angina diagnosed and coded by a cardiologist, are enrolled in the Clinical Pharmacy Cardiac Risk Service (CPCRS), a clinical pharmacy-managed, physician-monitored service that assists physicians with the implementation and management of evidence-based treatment strategies. One aspect of this care is to monitor lipid-lowering therapy to achieve appropriate lipid targets as recommended by National Cholesterol Education Program Adult Panel Treatment Panel III (ATP III) clinical practice guidelines.2,19

Both the PCCPS and CPCRS teams employ clinical pharmacists (BS or PharmD degree without residency training) and clinical pharmacy specialists (PharmD degree with specialized residency training). Members of these teams will be referred to here as clinical pharmacy services pharmacists (CPSPs). Approval to conduct this study was obtained from the KPCO Institutional Review Board.

Subject Selection

All active KPCO members of any age who received a prescription for simvastatin 10 mg to 40 mg daily between September 1, 2001, and February 28, 2002, were eligible for study inclusion. Patients were excluded if they were medically ineligible due to a previously documented intolerance or allergy to lovastatin, if their LDL-C was uncontrolled on simvastatin 40 mg, if they were on simvastatin 80 mg, or if it was deemed that the addition of nonstatin lipid-lowering therapy (e.g., fibrate, niacin) was more appropriate than converting to lovastatin to achieve lipid goals. In addition, patients were excluded if they received their prescriptions from non-KPCO pharmacies or if they or their primary care physician declined conversion. Potential study candidates followed in primary care were identified via KPCO primary care physician declined conversion. Potential study prescriptions from non-KPCO pharmacies or if they or their goals. In addition, patients were excluded if they received their more appropriate than converting to lovastatin to achieve lipid goals.2,19

Any patient without a fasting lipid panel (FLP), including total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides or alanine aminotransferase (ALT), was considered successful if the patient converted to lovastatin, with 2 or more cardiac risk factors, and without CVD and 1 or fewer cardiac risk factors based upon ATP III guidelines.2 The baseline LDL-C was the most recent LDL-C obtained while using simvastatin, but within 12 months of conversion to lovastatin. Final LDL-C was the LDL-C obtained from the first FLP performed at least 6 months after starting lovastatin. A conversion was considered successful if the patient converted to lovastatin, remained on the drug without reporting an adverse event for at least 6 months, and a final FLP was drawn.

Outcome Measures

The primary outcome for the study was the proportion of patients achieving their LDL-C goals after conversion to lovastatin (final) compared with their LDL-C results while on simvastatin (baseline). LDL-C goal was defined as <100 mg/dL, <130 mg/dL, and <160 mg/dL for patients with CVD, without CVD but with 2 or more cardiac risk factors, and without CVD and 1 or fewer cardiac risk factors based upon ATP III guidelines.2

Conversion guidelines were established based upon published literature comparing equivalent lipid-lowering doses of lovastatin and simvastatin.6,15,16 Most patients receiving simvastatin 10 mg, 20 mg, or 40 mg daily were converted to lovastatin 20 mg, 40 mg, or 80 mg daily, respectively. However, patients above or substantially below their LDL-C goal at the time of the conversion were converted to an adjusted dose if deemed appropriate by a CPSP and the subject's primary care physician. All patients were required to return to the laboratory for repeat FLP and ALT measurements at least 6 weeks after starting lovastatin. Based upon the follow-up FLP results, a CPSP adjusted the lovastatin dose if needed to attain the target LDL-C goal. If the LDL-C goal was not attainable on lovastatin or if a subject did not tolerate lovastatin, the subject was switched back to simvastatin, and/or an alternative medication (e.g., fibrate, niacin) was initiated. All therapeutic interventions were made according to ATP III clinical practice guidelines for cholesterol management and were approved by the patients' primary care providers. Patients or providers could refuse to change or request reconversion from lovastatin to simvastatin for any reason at any time.

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Secondary outcomes of the study were (1) the proportion of patients achieving their non–HDL-C (total cholesterol minus HDL-C) goal preconversion versus postconversion, (2) the change in mean LDL-C and non–HDL-C values preconversion and postconversion, (3) the proportion of patients who switched back to simvastatin due to intolerance or inability to achieve target LDL-C goals on lovastatin (therapeutic failure), (4) changes in drug acquisition and laboratory costs over 12 months (cost-minimization analysis), and (5) change in mean ALT levels (a surrogate measure of safety). In order to assess the therapeutic effects of conversion to lovastatin 80 mg from simvastatin 40 mg daily, we performed a subanalysis evaluating these outcomes for patients who underwent this conversion.

To assess whether differences in non–HDL-C or LDL-C control were attributable to differences in statin adherence, we performed a post hoc analysis on a sample of the patients converted from simvastatin to lovastatin. Adherence to simvastatin was calculated as a proportion of the quantity of tablets dispensed during the 12 months prior to the conversion date (a minimum of 3 refills in this time was required) divided by the number of days between the earliest simvastatin fill date during this time and the first prescription fill for lovastatin. The same method was used to calculate lovastatin adherence during the 12 months after the conversion date. To achieve 90% power to detect a 5% absolute difference in adherence rate with an alpha of 0.05, we needed 97 patients.

We performed cost-minimization analysis from the perspective of the payer to assess expenditure changes after the conversion project. Statin costs were calculated using representative group purchasing costs. This analysis took into account the number of tablets dispensed per 2-month supply (the standard KPCO quantity dispensed), including cases where patients used half tablets of simvastatin. The resultant cost savings were converted to per-member-per-year (PMPY) savings to provide a better measure of the cost impact to the organization. The FLP and ALT costs included test performance, phlebotomy costs, and a factor for the time a clinician spent evaluating the results. Follow-up laboratory tests performed after medication conversion were assumed to be an additional cost. Baseline laboratory costs were not included as these were considered part of usual care. One-way sensitivity analyses were performed by varying the costs of medications and laboratory tests between 50% and 150%.

To measure cost savings from our patients’ perspective, we calculated the average change in patient copays paid per year by subtracting the copay each patient would have paid for their lovastatin prescriptions over 1 year from what they would have paid for their simvastatin prescriptions over the same period.

Statistical Analysis
Descriptive statistics were utilized for the demographic data. McNemar’s test was utilized to test for differences in the proportions of patients achieving LDL-C and non–HDL-C goals before and after the intervention. The paired t test was utilized to examine mean changes in LDL-C, non–HDL-C, and ALT laboratory values preconversion and postconversion.

Results
A total of 7,637 patients receiving simvastatin were identified (Figure 1). Of these, 2,087 (27.3%) were excluded: 943 (12.3%) were medically ineligible (e.g., taking 80 mg simvastatin per day or had a history of intolerance to lovastatin), 543 (7.1%) refused to be converted, 491 (6.4%) were noncontinuous members, and 110 (1.4%) were unable to be contacted as outlined in Figure 1. The mean age of the 5,550 patients converted was 67 ± 10.8 years, 59% were male, and 53% were secondary prevention patients. The majority of patients (90.9%, n = 5,046) were successfully converted to lovastatin and had follow-up laboratory tests drawn, while 4.3% (n = 240) switched back to simvastatin. Of those converted successfully, 91.3% (n = 4,607) were converted to a lovastatin dose of equivalent potency to their baseline simvastatin dose.

Greater proportions of patients achieved LDL-C (P < 0.001) and non–HDL-C (P = 0.047) goals postconversion (final) compared with preconversion (baseline) (Figure 2). The largest change in control rate was seen in the primary prevention group. This likely reflects that this population had less intensive monitoring at baseline compared with secondary prevention patients who were enrolled in CPCRS. There were no significant changes or elevations in ALT values (Table 1).

Among all patients with preconversion and postconversion laboratory values, mean laboratory values (mean, 95% confidence interval [CI]) decreased as follows: LDL-C (-1.7, -1 to -2.4 mg/dL, P < 0.001); non–HDL-C (-3.2, -2.4 to -4 mg/dL, P < 0.001). Among patients converted to lovastatin 80 mg from simvastatin 40 mg, non–HDL-C decreased by -3.7 mg/dL (P = 0.001), but the mean LDL-C change (-1.3, -0.3 to -2.3 mg/dL, P = 0.058) was not significant.

We sampled 254 patients to assess statin adherence. Twelve were eliminated because they had fewer than 3 medication fills of either simvastatin or lovastatin during the evaluation period. The adherence rates for lovastatin and simvastatin in the remaining 242 patients were 93.8% (±14.7%) and 96.0% (±15.9%), respectively (P = 0.065).

The annualized statin cost savings from the conversion to lovastatin from simvastatin approximated $1.6 million, or $4.14 PMPY (Table 2). Reduced expenditure change persisted when drug or laboratory costs were varied from 50% to 150%.

We also evaluated expenditure changes from the patients’ perspective. The average annual savings per patient in reduced copayment after changing from brand simvastatin to generic lovastatin was -$145.29 (95% CI, $142.68-$147.90; P < 0.001) or 62%.
A goal of therapeutic conversion programs is to reduce overall health care costs without compromising therapeutic efficacy or patient safety. Our study demonstrated that this goal is achievable among a large number of patients, utilizing a pharmacist-directed conversion intervention. In our population of more than 5,000 patients, the proportion achieving LDL-C and non–HDL-C goals postconversion was higher than preconversion, although the clinical significance of the small improvement in quality is likely negligible. In the subgroup of patients converted to lovastatin 80 mg daily from simvastatin 40 mg, the proportion achieving non–HDL-C goals was also higher postconversion, indicating that simvastatin 40 mg does not have superior lipid-lowering effects compared with lovastatin 80 mg in actual clinical practice. The safety of lovastatin compared with simvastatin was supported by our findings that only 4.3% of patients switched back to simvastatin due to intolerance, and ALTs did not change.

Previous smaller studies have shown similar safety and efficacy results after statin conversion programs. Fugit and Resch evaluated lipids and safety measures after the conversion of 157 patients with (60.5%) and without CVD to lovastatin 10 or 20 mg daily from simvastatin 5 or 10 mg daily, respectively, by a pharmacist-managed hyperlipidemia clinic. After conversion, the percentage of patients at LDL-C goal was not significantly changed. Patel and colleagues converted 170 patients from pravastatin to lovastatin by implementing a therapeutic interchange program in a Veterans Affairs medical center. They found no significant difference in the percentage of patients at LDL-C goal (40% on pravastatin and lovastatin), and no significant differences in LDL-C values (118.0 mg/dL on pravastatin, 116.8 mg/dL on lovastatin). In contrast to our study, both of these previous studies had much smaller patient populations and therefore may not have been powered to detect a change. They also employed more labor-intensive patient management strategies, while our program utilized letters in many cases to notify patients of the medication change. Taylor and colleagues evaluated lipid control rates and safety in 942 patients converted from various statins to cerivastatin. They reported increased LDL-C control rates (64.8% to 74.5%, P < 0.001) and adverse events requiring drug discontinuation in 3% of patients, including 5 (0.6%) with myositis.

After conversion, 79.1% of all 5,046 patients who came in for follow-up laboratory tests achieved their LDL-C goals. This is a substantially higher lipid control rate than that described in other studies. A multicenter survey designed to evaluate lipid control in 4,888 primary- and secondary-prevention patients receiving lipid-lowering therapy...
found an LDL-C control rate of just 38.6%. Nationally, LDL-C control rates in patients with CVD (LDL-C goal <100 mg/dL) have been reported to be 47.6%. In contrast, 76.7% of our CVD patients had an LDL-C below goal, which is likely due to the close follow-up these patients receive with the CPCRS.

To date, there have been no reports published of therapeutic conversion programs specifically evaluating the conversion to lovastatin 80 mg daily from simvastatin 40 mg. In one comparative dose efficacy trial, lovastatin 40 mg twice daily (i.e., 80 mg per day) (n = 11) lowered LDL-C 48% versus a decrease of 41% by simvastatin 40 mg once daily (n = 61, the P value was not reported). Illingworth and colleagues reported a nonsignificant LDL-C decrease of 35% for lovastatin 80 mg versus 39% for simvastatin 40 mg daily in 24 patients participating in this cross-over study. Our study was not designed to directly compare the extent of LDL-C lowering for lovastatin versus simvastatin; however, the results of our subanalysis suggest similar efficacy of both agents on LDL-C and non-HDL-C without an increase in adverse effects.

The net cost savings from this statin conversion intervention, expressed across the entire membership of this HMO, was $4.14 PMPY after accounting for the additional laboratory costs. Our expenditure reduction was significant even though most of our patient population used half tablets of simvastatin at baseline, a strategy that has already been shown to reduce costs while maintaining lipid control. While drug-acquisition costs are unique to a given organization (e.g., Veterans Administration, Kaiser Permanente, pharmacy benefit managers), our results are generalizable to other managed care organizations, particularly as the gap widens between the actual acquisition cost for genericlovastatin versus the brand-drug simvastatin.

**Limitations**

A limitation of this study may be that not all patients were converted to an equivalent lovastatin dose from simvastatin. In 8.7% of cases, a CPSP recommended modifying the statin dose. However, our primary purpose was not to evaluate dose equivalency but rather to evaluate the conversion process and the proportion of patients who would remain at or reach their LDL-C goal through the conversion. We considered any FLP within 12 months prior to the conversion as “baseline” rather than obtaining a more recent lipid profile on all patients. While there may have been a number of patients who were not at their LDL-C goal immediately prior to the conversion, we were still able to demonstrate that a significant number of patients can reach or remain at their LDL-C goal after conversion to a less potent, less expensive statin if dosed appropriately.

The results of our study cannot be extrapolated to patients who have dyslipidemias not controlled on the maximum dose of simvastatin since these patients were excluded from our study. The cost savings observed in this study may not be fully

---

### TABLE 1

<table>
<thead>
<tr>
<th>Laboratory Measure</th>
<th>Preconversion Value</th>
<th>Postconversion Value</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LDL-C mg/dL</td>
<td>97.5 (96.8-98.2)</td>
<td>95.8 (95.1-96.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean non–HDL-C mg/dL</td>
<td>135.9 (135.0-136.8)</td>
<td>132.7 (131.9-133.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ALT IU/L</td>
<td>26.9 (26.4-27.4)</td>
<td>26.4 (26.0-26.8)</td>
<td>0.134</td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td>n=2,203 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LDL-C mg/dL</td>
<td>107.3 (106.1-108.5)</td>
<td>104.7 (103.6-105.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean non–HDL-C mg/dL</td>
<td>145.2 (143.8-146.6)</td>
<td>141.5 (140.3-142.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ALT IU/L</td>
<td>26.0 (26.0-27.0)</td>
<td>27.2 (26.6-27.8)</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td>n=2,843 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LDL-C mg/dL</td>
<td>89.6 (88.9-90.3)</td>
<td>88.8 (88.0-89.6)</td>
<td>0.112</td>
</tr>
<tr>
<td>Mean non–HDL-C mg/dL</td>
<td>128.3 (127.2-129.4)</td>
<td>125.7 (124.6-126.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ALT IU/L</td>
<td>27.2 (25.6-27.9)</td>
<td>25.8 (25.2-26.4)</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>Patients Converted to Lovastatin 80 mg</strong></td>
<td>n=2,235 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LDL-C mg/dL</td>
<td>94.9 (93.9-95.9)</td>
<td>93.6 (92.6-94.6)</td>
<td>0.058</td>
</tr>
<tr>
<td>Mean non–HDL-C mg/dL</td>
<td>134.7 (133.4-136.0)</td>
<td>131.0 (129.7-132.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ALT IU/L</td>
<td>26.9 (26.1-27.7)</td>
<td>26.5 (25.9-27.1)</td>
<td>0.498</td>
</tr>
</tbody>
</table>

* Paired t test.
† 95% confidence interval is provided in parentheses.
ALT = alanine aminotransferase; LDL-C = low-density lipoprotein cholesterol;
non–HDL-C = non–high-density lipoprotein cholesterol (total cholesterol minus HDL-C).

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### TABLE 2

<table>
<thead>
<tr>
<th>Primary Analysis*</th>
<th>Per-Member-Per-Year Expenditure Change ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross antihyperlipidemic drug costs†</td>
<td>(4.41)</td>
</tr>
<tr>
<td>Additional FLP and ALT lab costs ($20.25 each)‡</td>
<td>0.27</td>
</tr>
<tr>
<td>Net drug cost savings</td>
<td>(4.14)</td>
</tr>
</tbody>
</table>

**Sensitivity Analysis§**

| Simvastatin half tablets not used at baseline    | (8.37)                                   |
| Drug costs = 50%                                 | (1.94)                                   |
| Drug costs = 150%                                | (6.35)                                   |
| Lab cost = 50%                                   | (4.28)                                   |
| Lab cost = 150%                                  | 4.01                                    |

* Assumes 100% compliance with filled agent.
† Parentheses around a value indicate a reduction in annual expenditures.
‡ Includes cost of lab reagent, lab processing, and review time.
§ For total antihyperlipidemic drug and additional FLP lab costs; assumes 100% compliance with filled agent.
ALT = alanine aminotransferase; FLP = fasting lipid panel.
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reproducible in health care organizations that do not utilize lovastatin or are not structured to obtain group purchasing discounts on statin medications.

**Conclusion**

Our study provides evidence that a clinical pharmacy-directed program that converts dyslipidemia patients to generic lovastatin from brand simvastatin can result in reduced expenditures for both the health plan and for the patient while maintaining or improving lipid control and without increasing risk to the patient.

**ACKNOWLEDGMENT**

The authors wish to acknowledge the exceptional editorial and analytical assistance of Thomas Delate, PhD, clinical pharmacy research scientist, at Kaiser Permanente of Colorado, Aurora.

**DISCLOSURES**

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**REFERENCES**

Cost-Efficacy Analysis of Peginterferon alfa-2b plus Ribavirin Compared With Peginterferon alfa-2a plus Ribavirin for the Treatment of Chronic Hepatitis C

DANIEL C. MALONE, PhD; TRAM T. TRAN, MD; and F. FRED POORDAD, MD

ABSTRACT

OBJECTIVE: Combination therapy with pegylated interferon (Peg) and ribavirin (RBV) is the standard of care for the treatment of chronic hepatitis C virus (HCV) infection. This analysis compares the cost efficacy of treatment with pegylated interferon alfa-2b plus ribavirin (Peg-2b plus RBV) with pegylated interferon alfa-2a plus ribavirin (Peg-2a plus RBV) in hypothetical cohorts of 100 chronic HCV patients comprised 75% of genotype 1.

METHODS: A decision analysis model was constructed from the viewpoint of a managed care organization to compare Peg-2b plus RBV (1.5 mcg per kilogram per week plus RBV 800 mg per day) and Peg-2a plus RBV (180 mcg per week plus RBV 1,000-1,200 mg per kg) pursuant to the label dosing approved by the U.S. Food and Drug Administration. The model also included the so-called weight-based dosing regimen with Peg-2b plus RBV (1.5 mcg per kilogram per week plus RBV 10.6 mg/kg per kg). Patient weight was assumed to be 80 kg. For purposes of this analysis, early virologic response (EVR), defined as viral negative or 2-log drop in viral load, was assessed at 12 weeks for only genotype 1 patients, and nonresponders were assumed to discontinue therapy. The positive predictive value (PPV) was calculated for each treatment group for genotype 1 patients, which is determined from the values for EVR and sustained virologic response (SVR). Genotype 2 and genotype 3 patients were assumed to be treated for 24 weeks. Treatment duration and efficacy data were obtained from the published literature. Product pricing was based on average wholesale price, October 2004, and sensitivity analysis was performed using prices from the Federal Supply Schedule. Economic outcomes were determined from hypothetical 100-patient cohorts assumed to be comprised 75% of genotype 1 HCV.

RESULTS: Taking into account both EVR and SVR, the PPV for genotype 1 patients was 0.63 and 0.57 for Peg-2b plus RBV and Peg-2a plus RBV, respectively. The proportion of treated patients achieving SVR would be nearly identical, (53.6%) and (53.8%) for Peg-2a plus RBV and Peg-2b plus flat RBV, respectively. For Peg-2b plus weight-based RBV, the proportion of patients achieving SVR was higher (61.4%). Consequently, this leads to fewer overall treatment weeks for the Peg-2b plus RBV cohorts. Therefore, the cost per successful treatment (defined as: SVR) was 19.4% less ($37,638) for Peg-2b plus flat dosing of RBV as compared with Peg-2a plus RBV ($46,717). When Peg-2b plus RBV was dosed 1.5 mcg per kilogram per week plus RBV 10.6 mg/kg/day, then the cost per SVR was $39,045. The cost for the 100-patient cohort was $2,024,846 for Peg-2b plus RBV, $2,397, 529 for Peg-2b plus weight-based RBV, and $2,505,317 for Peg-2a plus RBV. This difference is due to a lower PPV in the Peg-2a plus RBV groups and hence more patients treated in spite of a low probability of achieving SVR.

CONCLUSION: The results of this cost-efficacy analysis suggest that treating HCV genotype 1 patients with Peg-2b plus RBV may result in savings to a health care system because fewer of these patients are treated beyond 12 weeks when achieving sustained viral clearance is unlikely.

KEYWORDS: Hepatitis C, Interferon, Peginterferon alfa-2a, Peginterferon alfa-2b, Cost-effectiveness

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Hepatitis C infection affects 4 million people in the United States and is a common cause of chronic liver disease and its sequelae, including cirrhosis and hepatocellular carcinoma. The hepatitis C virus (HCV) replicates rapidly, producing $10^{10}$ to $10^{12}$ viral particles a day. Eradication of the virus requires prolonged treatment with antiviral agents to eliminate the virus in the serum (phase 1 decay) and hepatocytes (phase 2 decay). Response to therapy is measured by a sustained virologic response (SVR), which is defined as the undetectable viral levels 6 months after completion of therapy (Table 1). The results of this cost-efficacy analysis suggest that treating HCV patients comprised 75% of genotype 1.
beyond 12 weeks, including reduction of treatment side effects, inconvenience, and cost from discontinuation of drug therapy at week 12.

Davis et al., in a subgroup analysis clinical trial reported by Manns et al., evaluated viral levels at 4, 12, and 24 weeks of therapy with peginterferon alfa-2b (Peg-2b) (PEG-Intron) plus RBV (Rebetol) and reported that when compared with baseline viral levels, a 2 log(10) (a 100-fold reduction) or greater drop in viral load at 12 weeks of therapy yielded a 72% positive predictive value (PPV) and a 100% negative predictive value (NPV) (see Table 1 for definitions of PPV and NPV). Similar analysis was performed on the peg-interferon alfa-2a (Peg-2a) (Pegasys) plus RBV (Copegus), with a finding of a 65% PPV and an 97% NPV. Therefore, if a 100-fold drop from baseline viral load was not achieved by week 12 of therapy, continuing treatment would be of no benefit because there would be little likelihood of response, and cost as well as side effects could be avoided. Differences in the predictability of viral clearance between Peg-2b and RBV and Peg-2a and RBV may lead to cost differences in treatment because a lower PPV will result in more weeks on treatment when the likelihood of success is low. In other words, a higher initial response (EVR) with a similar final outcome (SVR) means more individuals will be treated for the entire length of therapy even though they will not respond to treatment. Therefore, the purpose of this study was to evaluate the cost efficacy of Peg-2a and Peg-2b when combined with RBV for the treatment of hepatitis C using current practice management algorithms.

Methods

A decision analytic model was created to compare the cost efficacy of Peg-2a plus RBV (Pegasys + Copegus) and Peg-2b plus RBV (PEG-Intron + Rebetol). The perspective of the analysis was that of a health system (i.e., a managed care organization). The model was constructed to evaluate the costs and outcomes in a cohort of patients with hepatitis C (Figure 1). Three treatment options were evaluated: Peg-2a plus RBV, Peg-2b plus flat dosing of RBV, and Peg-2b plus weight-based dosing of RBV.

The financial time horizon for this particular model was 1 year because of the expected length of treatment for genotype 1. However, response to therapy is typically assessed at approximately 6 months after the last dose of medication. Previously published economic evaluations of hepatitis C therapy have been constructed using lifetime models and have not focused on the short-term costs and outcomes, which are particularly relevant to managed care organizations. Because the reported

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**TABLE 1** Definitions

| Early virologic response (EVR): a 2 log or greater reduction in hepatitis C RNA levels 12 weeks after the initiation of antiviral therapy. |
| Sustained virologic response (SVR): the absence of detectible hepatitis C RNA at least 20 weeks after completion of therapy. |
| Positive predictive value (PPV): the proportion of subjects who had 2 log or greater decrease in hepatitis C RNA levels at 12 weeks (early virologic response [EVR]) and also had a sustained virologic response (SVR) after completing therapy. Positive predictive value = true positive divided by true positive + false positive. For example: Among a total of 321 patients treated with Peg-2b, 229 had EVR at 12 weeks, with 145 resulting in SVR (true positives) and 84 being false positives. The positive predictive value can be calculated as: 145/(145+84) = 63%. |
| Negative predictive value (NPV): the proportion of patients who did not have a 2 log or greater decrease in hepatitis C RNA levels at 12 weeks (EVR) and did not achieve an SVR after completing therapy. Negative predictive value = true negative divided by true negative + false negative. In the above example, 92 (321-229) did not have an EVR at 12 weeks. No patients obtained an SVR if they did not have an EVR. The negative predictive value can be calculated as 92/(92+0) = 100%. |

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Because the reported adverse event profiles of these agents are similar, the costs associated with adverse events are not included in the model.

EVR = early viral response; SVR = sustained viral response.
adverse event profiles of these agents are similar, the costs associated with adverse events were not included in the model. The inclusion of treatment of side effects and related costs would increase the complexity of the model but would cancel across the therapies. We also did not include other costs of monitoring that would be similar for the 3 treatment regimens.

**Efficacy Data**

The efficacy data came from separate clinical trials involving Peg-2a plus RBV and Peg-2b plus RBV versus standard interferon combination therapy. Both trials were multicenter, multinational registration trials using similar study subjects in terms of patient characteristics. For Peg-2a, Fried et al. evaluated 180 mcg of peginterferon alfa-2a given weekly via subcutaneous injection plus daily RBV or placebo for 48 weeks. The RBV was dosed at 1,000 mg orally per day for those subjects 75 kg or less and 1,200 mg per day for those subjects weighing more than 75 kg. The comparison arm for this study was interferon 3 million units 3 times weekly plus RBV. Even though 3 groups were evaluated in this trial, the economic model was based upon the data for the Peg-2a plus RBV, the therapy arm of interest. The percentage of patients who discontinued therapy in the study was 22% for patients receiving Peg-2a plus RBV and 32% for both groups of interferon plus RBV and Peg-2a plus placebo, depending upon the therapy received. Because all efficacy analyses were based upon intent-to-treat after receiving at least 1 dose, the rate of discontinuation was accounted for in the efficacy analysis.

For Peg-2b, the clinical trial reported by Manns et al. had 3 arms, involving 2 different doses of peginterferon. One group was treated with peginterferon alfa-2b 1.5 mcg per kg given weekly subcutaneously plus 800 mg of RBV daily for 48 weeks. The second group was treated with peginterferon alfa-2b given at a dose of 1.5 mcg per kg weekly for the first 4 weeks of the study, followed by 0.5 mcg per kg for 44 weeks plus 1,000 to 1,200 mg per day of RBV orally. The third study group received interferon alfa-2b (Intron A) 3 million units subcutaneously 3 times per week plus 1,000 to 1,200 mg of RBV given daily. For the second and third arms, dosing of RBV was based upon subject weight, where those weighing less than 75 kg received 1,000 mg and those 75 kg or greater received 1,200 mg. In the United States, Peg-2b was approved based upon dosing of 1.5 mcg per kg for 48 weeks.

A subgroup analysis was performed by Davis et al. on the patients participating in the Peg-2b study (Manns et al.) who received doses of RBV that were at least 10.6 mg per kg per day, the so-called weight-based dosing regimen. This analysis found that the higher dose of RBV contributed to a higher response rate. This finding resulted in the weight-based dosing regimen becoming the standard of care outside the United States. The reported discontinuation rate in this study ranged from 13% to 14% depending upon the treatment arm. Efficacy assessment in this clinical trial was based upon intention to treat after the first dose received.

In the clinical trials reported by Manns et al. and Fried et al., SVR was the primary end point, defined as no detectable HCV RNA in the serum 24 weeks after cessation of drug therapy. In addition, both studies evaluated early viral response (EVR).

Davis et al., in the subgroup analysis of the Manns et al. trial, defined various thresholds as EVR and found that either a 1 or 2 log decline in HCV RNA at 12 weeks showed the highest sensitivity and also the highest NPV (excluding those persons who did not respond to treatment). For the present cost-efficacy analysis, we defined EVR as a 2-log decrease from baseline in HCV RNA levels after 12 weeks of treatment. Consequently, the PPV of EVR affects the overall cost of treatment when treatment is adjusted according to the EVR results. PPV is defined as the likelihood of achieving SVR among those persons who do achieve a rapid virologic response. Evaluating the EVR is important for those patients with the genotype 1 virus because patients destined to fail therapy can be discontinued early. The 12-week rule in genotypes 2 and 3 is less useful because of the shorter treatment course and higher response rates. In fact, it is being modified to a 4-week assessment, or rapid virological response (RVR). Thus, this model specifically accounts for the ratio of genotype 1 to genotype 2 or genotype 3 in both studies and the PPV in response to treatment for persons with genotype 1.

**Model Specification**

The primary model examined 2 hypothetical cohorts of 100 HCV subjects receiving either Peg-2a or Peg-2b. One cohort received 180 mcg weekly of Peg-2a plus RBV 1,000 to 1,200 mg daily, the second received 1.5 mcg weekly of Peg-2b plus 800 mg of RBV daily (so-called flat dosing). We also extended the model to include a third cohort that reflects dosing not approved for the product label in the United States in which patients receive 1.5 mcg weekly of Peg-2b plus 10.6 mg/kg of RBV daily (the so-called weight-based dose). For all 3 cohorts, a patient weight of 80 kg was assumed. The proportion of patients with genotype 1 was assumed to be 75%. This value is higher than those reported in clinical trials with peginterferons, but it was believed to be more representative of the U.S. population because the clinical trials were conducted internationally and genotype 1 has a high prevalence in the U.S. as compared with some other parts of the world where the clinical trials were conducted. For example, prevalence of genotype 1 is 48.7% in Belgium and 57.9% in France. Prevalence of type 1 genotype HCV is similar in Japan and the United States, but lower in Brazil, Vietnam, and Indonesia.

For those subjects with non-genotype 1, it was assumed that treatment lasted 24 weeks. For genotype 1 patients, it was assumed that viral response was assessed at 12 weeks. Those patients who had a decrease of 2 logs or more in viral load were

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assumed to have received an additional 36 weeks of therapy, for a total of 48 weeks. For patients who did not have a viral response, it was assumed that treatment was stopped at 12 weeks.

The outcomes for this study were the number of patients having an SVR, the cost per SVR, and the incremental cost-effectiveness ratio per SVR.

### Results

Patient characteristics in the 3 treatment groups in the 2 clinical trials were similar except for patient weight, which was considerably lower in the weight-based RBV and Peg-2b group compared with the others (Table 2). Patients in this weight-based RBV group were those who received at least 10.6 mg/kg of RBV, and, since the dosing regimen was 800 mg for all patients, they were, by definition, lighter in average body weight. Across the 3 groups, the percentage of patients that were genotype 1 ranged from 65% to 68%.

Table 3 shows the SVR for all subjects and for genotype 1 subjects across the 3 groups. SVR among genotype 1 subjects was higher for Peg-2a (46%) than Peg-2b flat dose (42%), but Peg-2b with weight-based dose RBV had the highest SVR (48%). However, these SVRs were not significantly different from each other based upon the 95% confidence intervals.

Peg-2a had the highest EVR, with 81% of genotype 1 subjects having an EVR, compared with 71% for Peg-2b and 65% for Peg-2a with weight-based RBV.

The model took into account only the costs of peginterferon and RBV since all other treatment resources would be similar. Medication costs were based upon average wholesale price (AWP) as listed by Medispan (effective October 2004). The price of Peg-2a was $401.04 per dose. For Peg-2b, the 120 mcg dose was $406.94. The 120 mcg dose of Peg-2b was selected because this strength is recommended for patients weighing between 61 to 85 kg when receiving combination therapy with RBV. The price of RBV has been affected by the patent expiration, but at the time of this analysis (October 2004), the prices for generic formulations were higher than for the brand-name (Copegus). Therefore, we used the brand-name price for RBV, which was $6.64 per 200 mg capsule. Managed care organizations typically reimburse pharmacies or purchase pharmaceuticals at substantially less than AWP. To account for this, we conducted a sensitivity analysis using AWP minus 17%. Under this situation, the costs were $332.86 for Peg-2a (83% of $401.04), $337.76 for Peg-2b (83% of $406.94), and $5.50 for RBV (83% of $6.63).

Another sensitivity analysis was conducted using the Federal Supply Schedule prices (FSS) as obtained from the Department of Veterans Affairs Pharmacy Benefits Management Group. Product pricing under the FSS was $143.30 for Peg-2a, $126.53 for Peg-2b, and $1.00 per dose for RBV. The FSS, with its best price provision, represents the lowest prices that the government or any managed care organization would pay for these products (excluding donated products or samples).

Sensitivity analyses were conducted to determine the impact of variable uncertainty on the models. One-way sensitivity analyses were performed. Threshold analysis was done for the key parameters of PPV and peginterferon costs. Threshold analysis is a 1-way sensitivity analysis where a parameter is varied until a break-even point is reached, ignoring the plausible range for that particular variable.

### Table 2 Patient Demographics From Clinical Trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Peginterferon alfa-2a</th>
<th>Peginterferon alfa-2b</th>
<th>Peginterferon alfa-2b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>180 mcg + 1,000 to 1,200 mg</td>
<td>1.5 mcg/kg + 1,000 to 1,200 mg</td>
<td>10.6 mg/kg + 10.6 mg/kg</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>N = 453</td>
<td>N = 511</td>
<td>N = 188</td>
</tr>
<tr>
<td>Sex: male/female (% male)</td>
<td>324/129 (72)</td>
<td>321/90 (63)</td>
<td>NR</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.8 ± 10.1</td>
<td>43.9 ± 8.0</td>
<td>42.8 ± 8.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.8 ± 17.5</td>
<td>82.4 ± 18.0</td>
<td>64.5 ± 7.5</td>
</tr>
<tr>
<td>Mean HCV RNA in serum (copies/ml × 10^6)</td>
<td>6.0</td>
<td>6.4 ± 0.6</td>
<td>6.3 ± 0.6</td>
</tr>
<tr>
<td>Genotype 1: n (%)</td>
<td>298 (65)</td>
<td>348 (68)</td>
<td>122 (65)</td>
</tr>
</tbody>
</table>

**Notes:**
- Davis et al. is a subgroup analysis of the trial reported by Manns et al.
- NR = not reported.

### Table 3 Virologic Response and Positive Predictive Value for Treatment Regimens

<table>
<thead>
<tr>
<th>Treatment Response</th>
<th>Peginterferon alfa-2a</th>
<th>Peginterferon alfa-2b</th>
<th>Peginterferon alfa-2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virologic response (SVR) for all HCV genotypes (%)</td>
<td>254 (56%)</td>
<td>274 (54%)</td>
<td>114 (61%)</td>
</tr>
<tr>
<td>Sustained virologic response (SVR) for HCV genotype 1 only (%) [95% CI]</td>
<td>136/296 (46%) [40%-52%]</td>
<td>145/348 (42%) [37%-47%]</td>
<td>59 (48%) [39%-57%]</td>
</tr>
<tr>
<td>Early virologic response (EVR) at 12 weeks for HCV genotype 1 only (%) [95% CI]</td>
<td>241/298 (81%) [77%-85%]</td>
<td>229/321* (71%) [66%-76%]</td>
<td>90/122 (74%) [66%-82%]</td>
</tr>
<tr>
<td>Positive predictive value (PPV) for genotype 1 only [95% CI]</td>
<td>0.57 [0.51-0.63]</td>
<td>0.63 [0.58-0.68]</td>
<td>0.65 [0.63-0.79]</td>
</tr>
</tbody>
</table>

**Notes:**
- *12-week viral data were available for only 321 subjects.
- CI = confidence interval; HCV = hepatitis C virus.

**Results**

The outcomes for this study were the number of patients having an SVR, the cost per SVR, and the incremental cost-effectiveness ratio per SVR.
showing a response to therapy after 12 weeks (Table 3). For Peg-2b, the EVR was 71% for flat RBV dosing and 74% for weight-based RBV dosing. The PPV for Peg-2a for genotype 1 was 57%, as compared with 63% and 65% for Peg-2b flat and weight-based dosing, respectively (Table 3). Thus, even though Peg-2a has a larger percentage of genotype 1 patients that have an initial viral decline (at week 12), the relapse rate is higher, and, hence, the overall SVR for Peg-2a (40% to 52%) is similar to Peg-2b (37% to 47%) for flat dosing of RBV and 39% to 57% for weight-based dosing of RBV (see Table 3). It is important to note that, in the clinical trials, the EVR stopping rules were not in place. Thus, all genotype 1 patients were assigned to receive 48 weeks of treatment. The important variable that influences the results of this study is that because of the higher EVR for Peg-2a, more patients are treated who are unlikely to benefit, which increased the cost for the Peg-2a cohort.

Estimates of the direct drug cost of each treatment regimen and genotype are shown in Table 4. For all 3 treatment regimens, the drugs costs of treatments are fairly similar, with a full year (48 weeks) of treatment for each genotype 1 patient from $28,444 to $32,999 and from $14,222 to $16,450 for each genotype 2 or 3 patient for 24 weeks of drug therapy.

The results from the economic analysis are shown in Table 5. The costs of drug therapy for each 100-patient cohort ranges from $2.02 million for Peg-2b + fixed dose RBV to $2.51 million for Peg-2a + RBV. The difference in cost was a result of total number of weeks on therapy: 3,687 weeks of therapy for Peg-2a compared with 3,417 for Peg-2b flat or 3,498 for weight-based regimens. The difference in cost for a cohort of 100 patients between Peg-2b flat dosing and Peg-2a is $480,000. This $480,000 is equivalent to an additional 17 genotype 1 patients being treated for 48 weeks using Peg-2b + fixed-dose RBV.

The proportion of patients who achieve SVR was similar among Peg-2a (53.63%) and Peg-2b flat dosing (53.80%), and higher for Peg-2b weight-based dosing (61.41%). There was a difference of almost 8 patients between Peg-2b plus flat RBV and weight-based RBV treatments. The cost to achieve a successfully treated patient, defined as having an SVR, was lowest with Peg-2b flat dosing at a cost of $37,638. Peg-2b weight-based RBV dosing had a cost/SVR of $39,045, and Peg-2a had a cost/SVR of $46,717. The incremental cost-effectiveness of using Peg-2b weight-based dosing over Peg-2b flat dosing was $48,989 for each additional patient obtaining an SVR. Peg-2a, still more than for Peg-2b flat or weight-based dosing. The incremental cost-effectiveness ratio was $138,265 per successful outcome. The threshold value for Peg-2a PPV was 0.78, which was well beyond the 95% confidence interval of 0.51 to 0.63. Another analysis evaluated the PPV of Peg-2b flat dosing. When the PPV is only 0.43, then the cost per successful outcome for Peg-2a and Peg-2b flat dosing is nearly identical. Again, this is well beyond the 95% confidence interval for the PPV for Peg-2b flat dosing.

Other sensitivity analyses were conducted examining the cost of the various treatments. If product pricing was at AWP minus 17%, then the cost per successfully treated patient for the 3 treatments was $31,240, $32,407, and $38,775 for Peg-2b flat dosing, Peg-2b weight-based dosing, and Peg-2a, respectively. In the incremental analysis, use of Peg-2a was less cost effective than Peg-2b and weight-based dosing of RBV. When FSS prices are applied to all therapies, including the price of RBV, the lowest cost per successfully treated patient was Peg-2b weight-based dosing ($12,630 per successfully treated patient). Peg-2a was only $110 more, at $12,740 per SVR, while Peg-2b flat dosing was $13,193 per SVR. Using FSS prices, Peg-2b plus flat RBV dosing had the lowest cohort cost ($528,029 versus $683,201

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**Sensitivity Analysis**

One-way sensitivity analyses were conducted to evaluate the input of key parameters on the model. One of the key parameters for the model was the PPV for genotype 1. If the PPV for Peg-2a is increased from 0.57 to 0.63, then the number of successfully treated patients for Peg-2a was 57.27, an increase of 3.64. The resulting cost per successfully treated patient was $43,744 for Peg-2a, still more than for Peg-2b flat or weight-based dosing. The incremental cost-effectiveness ratio was $138,265 per successful outcome. The threshold value for Peg-2a PPV was 0.78, which was well beyond the 95% confidence interval of 0.51 to 0.63. Another analysis evaluated the PPV of Peg-2b flat dosing. When the PPV is only 0.43, then the cost per successful outcome for Peg-2a and Peg-2b flat dosing is nearly identical. Again, this is well beyond the 95% confidence interval for the PPV for Peg-2b flat dosing.

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for Peg-2a). Under FSS pricing, Peg-2a was again more costly and less effective than Peg-2b flat- and weight-based dosing regiments.

A threshold analysis was conducted varying the AWP price of Peg-2a. When it was reduced to $269 (a reduction of $138 [34%]) per 180 mcg, then the cost per successfully treated patient was identical for Peg-2a and Peg-2b flat dosing. Varying patient weight to the lower and upper bounds of the 95% confidence interval as well as varying the proportion of genotype 1 patients to 50% did not affect the rank order of the results in terms of cost per successfully treated patient.

Discussion

The results from this cost-efficacy study suggest that treatment with Peg-2b may be less costly than with Peg-2a for a cohort of subjects with HCV who are eligible for treatment. Although both Peg-2a and Peg-2b have demonstrated similar SVR overall and by genotype, for genotype 1, there is a significant difference in EVR rates between Peg-2a and Peg-2b flat dosing. In this analysis, the higher EVR for Peg-2a among genotype 1 patients leads to more treatment but with no additional benefit over those treated with Peg-2b flat- or weight-based dosing. Consequently, the cost per successful treatment is lower with Peg-2b combination therapy as compared with Peg-2a combination therapy. The results of the sensitivity analyses indicated that efficacy rates or costs would have to change substantially to affect the rank order of the products.

Pegylated interferon plus RBV is now the standard of care for the treatment of chronic hepatitis C. Durable viral eradication is possible with effective therapy in more than 50% of patients; however, cost and side effects may limit the number of patients successfully treated. Viral kinetic studies have shown that once interferon therapy is initiated, an early rapid initial decline in viral levels, termed phase 1 decay, is noted, but this decline does not correlate well to eventual viral clearance. It is the subsequent phase 2 decay that takes place over the next several weeks that reflects the death rate of infected hepatocytes and does correlate with sustained virologic response. This understanding of the viral kinetic profile led to analysis of the viral response at 12 weeks into therapy in both pivotal pegylated interferon plus RBV trials. From these data, PPVs and NPVs have been determined; Peg-2b has a higher PPV than does Peg-2a, with a similar NPV. The economic differences are a function of this difference in PPV.

Quantitative HCV RNA testing has become widely available and has made the clinical use of viral load feasible. Although there are some limitations to these tests, including different assays and limited dynamic linear ranges of the tests, there are now important clinical applications to testing. Prior to initiating therapy, a baseline viral load should be obtained. In the genotype 1 patient, after 12 weeks of therapy another viral load is obtained and compared with the patient’s baseline viral load. If an EVR, defined as at least a 2 log 10 drop from baseline viral load, is achieved, then the patient should be continued on therapy because they have a good chance of SVR at the end of follow-up. If, however, an EVR is not achieved at 12 weeks, an SVR is highly unlikely, and the patient should not be put through the cost and potential side effects of the full 48 weeks of treatment.

In some clinical scenarios, such as the patient with advanced fibrosis or extrahepatic hepatitis C disease, patients may be continued on therapy with modified doses of interferon, not with the goal of viral eradication but with the goal of viral suppression. Current ongoing prospective studies will assess the utility of this practice.

A recent article by Mangia et al. reported the results of testing for HCV RNA levels at week 4 for genotype 2 and 3 patients treated with Peg-2b plus RBV. The study had 2 primary groups: 24 weeks of treatment or HCV RNA testing at 4 weeks. For the group with 4-week HCV RNA assessments, treatment was continued for either 12 or 24 weeks depending upon the result of the test (undetectable levels resulted in 12 weeks of additional therapy; whereas HCV positive patients continued treatment for 24 weeks). The overall response rate for early response was 62% versus 64% for usual treatment for 24 weeks (with no HCV RNA testing). The response rate with 12 weeks of therapy in those with EVR was 85% compared with 91% (not significant) with 24 weeks of therapy. This means that two thirds of patients with genotype 2 and 3 will be able to be treated successfully with 12 weeks of therapy with Peg-2b plus RBV.

The use of the EVR applies to all genotypes; however, since recent data have shown an excellent response to only 24 weeks of therapy in genotypes 2 and 3, the use of the 12-week EVR is not of significant cost benefit. It is mainly in the more difficult-to-treat genotype 1 patients who require ≥8 weeks of therapy that an early-stopping rule is most useful. The 2002 National Institutes of Health Consensus Development Conference Statement on Hepatitis C has recommended the use of EVR stopping rules, and prospective validation of these data is forthcoming in ongoing studies. Consequently, the economic rationale for using one peginterferon over another is based not solely on EVR but, rather, the likelihood that patients will respond to the full course of therapy. Therefore, even though Peg-2a has an initial higher EVR than Peg-2b, there is no difference in SVR achieved when compared with Peg-2b, making the latter a more cost-effective therapy.

In our analysis, using the published data from the Manns et al. and Fried et al. clinical trials, the calculated PPVs and EVR data led to a difference in our theoretical cohort of number of patients who continued on therapy after an EVR was achieved but would not ultimately achieve an SVR. Therefore, in this cost analysis, it was more costly to treat a cohort of 100 patients with Peg-2a and RBV because more patients were continued on therapy who did not ultimately achieve viral eradication. The reason for this difference may be related to the higher relapse rates noted in the Peg-2a trial.
Previous economic analyses have examined Peg-2a plus RBV and Peg-2b plus RBV as compared with standard interferon therapy plus RBV. Most of these studies were conducted using international cost data, with Sullivan et al. using cost structures from Italy; Buti et al. based upon structures from Spain; and Siebert et al. using a German perspective. Wong et al. and another paper by Sullivan et al. use cost values that were specific to the U.S. market. All analyses found that peginterferon plus RBV was cost effective relative to standard interferon plus RBV. Wong et al. found that Peg-2b was incrementally cost effective compared with interferon alfa-2b, at a cost of $13,600 to $22,800 per quality-adjusted life-year (QALY). The U.S.-based analysis by Sullivan et al. found that the incremental cost-effectiveness ratio of Peg-2a plus RBV compared with interferon alfa-2b was $2,600 per QALY. The other economic analyses have found similar costs (approximately $10,894/QALY in Italy; 3,760/QALY in Spain; and 6,600/QALY in Germany).

By conventional standards, peginterferon is cost effective relative to standard interferon. Therefore, the decision becomes one of which peginterferon to use.

**Limitations**

This analysis was based on publicly available information at the time the study was conducted and data from 2 large clinical trials. One of the clear limitations, therefore, is the differences in study criteria and patient populations, although most patient characteristics were fairly similar (Table 2). In the clinical study by Freid et al., study patients were eligible if they met the following criteria: were interferon naïve; had at least 2,000 copies of HCV RNA per milliliter of serum, their serum alaninotransferase activity was greater than the upper limit of normal within 6 months of study entry; and they had a liver biopsy result consistent with the diagnosis of chronic hepatitis C. Patients were excluded from the study if they had any of the following: neutropenia, thrombocytopenia, anemia, HIV infection, decompensated liver disease, serum creatinine level greater than 1.5 times the upper limit of normal, poorly controlled psychiatric disease, alcohol or drug dependence within a year of entering the study, or a substantial coexisting medical condition. The criteria for entry into the Manns et al. study included the following: previously untreated adult patients with a liver-biopsy-confirmed diagnosis of chronic hepatitis C; serum alanine aminotransferase levels above the upper limit of normal; absence of neutropenia, anemia, or thrombocytopenia; and bilirubin, albumin, and creatine within normal limits. Patients were excluded from the Manns et al. trial if they had any of the following: decompensated cirrhosis, serum alpha-fetoprotein of more than 50 µg per liter, HIV infection, previous organ transplantation, other causes of liver disease, hemophilia, poorly controlled diabetes, and autoimmune disorders; if they were unable to use contraception; or had any of the following diseases or conditions: psychiatric disease, seizures, cardiovascular disease, or hemoglobinopathies. In general, these inclusion and exclusion criteria are comparable between the studies.

Second, this analysis excluded consideration of adverse events that may result from treatment. The types of adverse events experienced by patients exposed to interferon and peginterferon are similar, but the actual frequency of specific adverse events may vary. For example, fever was reported in 43% of subjects receiving Peg-2a and 46% of subjects receiving Peg-2b. The incidence of neutropenia was 20% for Peg-2a and 18% for Peg-2b. In addition, criteria for classifying adverse events was not well defined in the publications for either trial. Finally, there have been no published data of large studies (>60 patients per group) comparing Peg-2a and Peg-2b in a head-to-head fashion, though a multicenter, randomized study is currently ongoing. Until data are available from these direct-comparison studies, economic analyses need to be based upon the existing available evidence to assist in the efficient allocation of resources.

Another issue with decision models is the use of deterministic cost data, and especially the use of the AWP. To overcome this limitation, we used a price of AWP minus 17% and also prices from the FSS to represent the range of possible costs for managed care organizations. These analyses also included changing the cost of RBV. Organizations should carefully evaluate this model in context with the prices actually paid for these agents and other factors that may influence product use.

**Conclusion**

This study found that the use of Peg-2b and RBV may be preferred to Peg-2a because of its lower cost of treatment for a hypothetical cohort of 100 HCV patients. The primary factor in the analysis was the difference in EVR and PPV, which led to fewer genotype 1 patients in the Peg-2b cohort continuing treatment when there was a very low likelihood of eventual sustained virologic response.

**DISCLOSURES**

Funding for this research was provided by Schering-Plough Pharmaceuticals, Inc. and was obtained by author Daniel C. Malone. Malone discloses that he is a consultant to Schering Plough; author Tram T. Tran discloses that she has received grants and honoraria from Schering Plough; F. Fred Poordad discloses that he has received grants and honoraria from and done research for Schering-Plough.

Malone served as principal author of the study. Study concept and design were contributed by Malone and Tran. Analysis and interpretation of data were contributed by all authors; statistical expertise was contributed by Malone. Drafting of the manuscript was primarily the work of Malone, and its critical revision was the work of all authors. Administrative, technical, and/or material support was provided by Jaime Pew, Schering-Plough.

**REFERENCES**


Cost-Efficacy Analysis of Peginterferon alfa-2b plus Ribavirin Compared
With Peginterferon alfa-2a plus Ribavirin for the Treatment of Chronic Hepatitis C


A Review of the Use of CAM Therapy and the Sources of Accurate and Reliable Information

MARY McHUGHES, MS, PharmD, and BARBARA N. TIMMERMANN, PhD

ABSTRACT

OBJECTIVE: To describe how pharmacists can answer the call by the Institute of Medicine (IOM) of the National Academies to become more involved in evaluating complementary and alternative medicine (CAM) and to suggest resources pharmacists can access to be better prepared to advise their patients about these therapies.

SUMMARY: Information published by the IOM in January 2005 clearly indicates that the American public considers CAM therapies increasingly to be “conventional” lifestyle choices rather than “alternative” practices. Some managed care organizations (MCOs) have offered CAM services for at least 8 years, and one of the nation’s largest MCOs created a network of CAM providers in 2003 with a 30% discount on provider fees. Pharmacists report an increase in questions regarding the use of herbal products and dietary supplements. As experts in drug-drug interactions, there is the expectation that pharmacists are a source of information for drug-herb interactions. Yet some surveys show pharmacists are uncomfortable answering questions about these products because, although there is an increase in the integration of CAM and conventional medicine, there are few scientific studies available to guide the clinical decisions that are necessary. The Office of Dietary Supplements (ODS) and the National Center for Complementary and Alternative Medicine (NCCAM) have increased funding of CAM research. There is a particular need for clinicians to become involved in assessing the safety and efficacy of these products. At least one health plan has created, through its pharmacy and therapeutics committee, a scientifically based, pocket-sized CAM guide through its pharmacy and therapeutics committee, a scientifically based, pocket-sized CAM guide that clinicians rated as somewhat to very helpful as a counseling aid.

CONCLUSION: With the increasing volume of information on CAM aimed at consumers by the press, television, Internet, and other media, it is critical for pharmacists to remain current in their knowledge. Pharmacists should know what the IOM is saying about CAM and develop relationships with the CAM pharmacists to remain current in their knowledge. Pharmacists should know what reliable information resources are available and be able to evaluate the literature to help patients and providers interpret what they read and hear. It is important for pharmacists to have access to and be involved in ongoing evaluation of CAM therapies being used by so many people.

KEYWORDS: Complementary and alternative medicine, Pharmacy practice, Dietary supplements, Herbs, Botanicals, Pharmaceutical care, Information management, Clinical trials, NCCAM, IOM, NIH, ODS

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A recent article published in the *Journal of Managed Care Pharmacy* described the development of a scientifically based, pocket-sized CAM guide through its pharmacy and therapeutics (P&T) committee that clinicians rated as somewhat to very helpful as a counseling aid. The National Center for Complementary and Alternative Medicine (NCCAM), one of 27 institutes and centers making up the National Institutes of Health (NIH), defines CAM as “a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine.”

A 1990 national survey (1,539 adults contacted via telephone, with a 67% response rate) documented the prevalence, cost, and patterns of use of alternative medicine in the U.S. health care system. One in 3 respondents (34%) reported using at least 1 unconventional therapy in the past year, and a third of these had met with providers of unconventional therapy. Frequency of use of these therapies varied among sociodemographic groups. The highest use was found among nonblack respondents aged 25 to 49 years with more education or higher incomes. The majority reported using unconventional therapies for chronic medical conditions. Extrapolating the results suggests that, in 1990, Americans made an estimated $425 million (95% confidence interval, $302-$548 million) visits to providers of unconventional therapy, a number exceeding the count of all visits to U.S. primary care physicians ($388 million). The associated 1990 expenditures for these unconventional therapies were approximately $13.7 billion, three quarters of which ($10.3 billion) was paid out of pocket. This is comparable to out-of-pocket expenditures for all hospital care in the United States in 1990 ($12.8 billion) and nearly half the out-of-pocket payments for physicians’ services ($23.5 billion). Other survey data confirm the extensive and growing use of CAM. Ten percent of survey respondents in 1994 and 42% in a public opinion poll in 1997 reported use of alternative medicine in the United States. The aforementioned national telephone survey conducted in 1990 was repeated by Eisenberg et al. in 1997 (2,055 adults contacted, with a 60% weighted response rate) and revealed an increase in CAM use from 33.8% in 1990 to 42.1% in 1997 (P ≤0.001). Therapies showing the most increase in use between 1990 and 1997 included herbal medicine, massage, megavitamins, self-help groups, folk remedies, energy healing, and homeopathy. Kessler and colleagues’ analyzed Eisenberg’s 1997 dataset, this time focusing on questions about first-time use of CAM by all individuals aged 18 years and older. These data are shown in Figure 1,
visits to primary care physicians. An estimated 15 million adults take herbal remedies or high-dose vitamins along with prescription drugs. The annual out-of-pocket costs for CAM are estimated to exceed $27 billion.

The Centers for Disease Control and Prevention's National Center for Health Statistics released a report based on its 2002 National Health Interview Survey in May 2004. The data were collected from a nationally representative sample of U.S. adults aged 18 years and older and a total of 31,044 interviews. Statistics were age-adjusted to the year 2000 U.S. standard population. When excluding prayer specifically for health reasons, the data show that 36% of adults had used some form of CAM therapy during the previous 12 months, most often to treat back pain or back problems, head or chest colds, neck pain or neck problems, joint pain or stiffness, and anxiety or depression. Using conservative assumptions about fees charged by alternative therapy practitioners, Eisenberg et al. estimated that Americans spent $21.2 billion on visits to these practitioners in 1997, of which at least $12.2 billion was paid out of pocket. This exceeds actual 1997 out-of-pocket expenditures of $11.1 billion for all hospitalizations and is more than half the amount of actual out-of-pocket payments for all physician services the same year, $21.6 billion.

Including herbal remedies, megavitamins, diet products, and alternative therapy books, classes and equipment, total out-of-pocket expenditures related to alternative therapies in 1997 were estimated at $27 billion, a figure comparable to projected out-of-pocket expenditures for all U.S. physician services that year. Clearly, the American public considers CAM therapies less as “alternative” practices and increasingly as “conventional” lifestyle choices. This widespread increase in use parallels increasing safety concerns. These concerns are expressed in terms of product quality and safety as well as benefit/risk. With respect to the latter, historically safe use of herbal remedies and botanical supplements does not include current society’s use of prescription and over-the-counter agents. People not only take these agents concomitantly with botanicals, but they also tend not to tell their health care providers about such use. In both the 1990 and 1997 surveys by Eisenberg et al., fewer than 40% of CAM therapy users reported disclosing their use of these therapies to their physicians.

A recent review by Izzo and Ernst reveals the potential for fatal consequences when herbal products interact or interfere with the normal pharmacology of some pharmaceutical drugs. The most readily recognized drug-drug or drug-botanical interactions are those involving cytochrome P450 (CYP 450) enzymes. Consideration of these interactions in early drug development has been difficult because of uncertainty about whether the atypical kinetic behavior exhibited in vitro is clinically relevant. Yet understanding drug metabolism is critical to measuring the effect a drug will have in vivo. A confounding problem with herbal or specialty combination products is that each can...
contain a multitude of naturally occurring chemicals that may either inhibit or induce the CYP 450 system. Evaluating various herbal products with such assays is an example of current research funded by NCCAM.17

**Integrative Medicine**

Maizes et al. define integrative medicine as “medicine that reemphasizes the relationship between patient and physician, and integrates the best of complementary and alternative medicine with the best of conventional medicine.”18 Berndtson19 defines the term in a similar way, emphasizing the use of evidence. Whatever the definition, integrative medicine reflects the growing recognition by health care practitioners that many factors contribute to the health and well-being of individuals and the public. For example, in order to ascertain whether quantitative electroencephalography could detect differences between medication and placebo responders, 2 independent, double-blind, placebo-controlled studies examined brain function in depressed subjects receiving either an antidepressant or a placebo.20 Both placebo and antidepressant responders exhibited alterations in prefrontal brain function; however, these changes were distinctly different. Placebo responders showed a significant increase in prefrontal cerebral perfusion starting early in treatment. This was not seen in medication responders, who showed a decrease in prefrontal cerebral perfusion, or in nonresponders, medication or placebo, who showed no significant change. The authors suggest that future studies use brain function measures to explore the distinguishing features of placebo effects and investigate mechanisms by which placebo treatments might reduce depressive symptoms. It is important to remember that whether people are healthy or not has to do “not only with disease and illness, but also with who we are, where we live and work, and the social and economic policies of our government.”21

In 1998, the American Hospital Association (AHA) began surveying hospitals on CAM services and found that only 6% of hospitals offered such services. By 2001, 15% of hospitals offered CAM services. When the AHA asked hospitals why CAM services were being offered, 49% indicated that it was in response to patient demand; integrative medicine is being driven by the consumer.

Cancer treatment centers frequently offer CAM therapies. The University of Texas M.D. Anderson Cancer Center supports an integrative medicine approach incorporating research, education, and a clinical program. “Place … of wellness offers more than 75 complementary therapy program opportunities, free of charge, to help with the nonmedical issues of living with cancer. It is a bridge between standard medical care and spiritual healing that we call complementary and integrative medicine.”22 The Memorial Sloan-Kettering Cancer Center and the Dana Farber Cancer Institute also have integrative medicine centers. In 2003, a nonprofit organization of health professionals, the Society for Integrative Oncology, was created to provide a “convenient forum for presentation, discussion and peer review of evidence-based research and treatment modalities in the discipline known as integrative medicine” in cancer care.23

Several attempts have been made to quantify use of CAM by conventional health care practitioners. Overall, interest is high, and many primary care physicians believe some of these therapies are useful adjuncts to conventional treatments.10(p.202)

As of December 2004, 22 medical centers in the United States belonged to the Consortium of Academic Health Centers for Integrative Medicine.10(Appendix B) Many of these centers offer fellowships for physicians who want to incorporate CAM therapies into their practices. The University of Arizona’s Program in Integrative Medicine was founded in 1994 by Andrew Weil, MD. In 1997, this program’s faculty included a clinical pharmacist, the late Kathryn Grant, PharmD. Grant attended patient care conferences and worked with the first 4 physicians on fellowship in the program to incorporate allopathic and alternative remedies, while researching alternative treatments. In August 2004, Tieraona Low Dog, MD, joined the faculty of this program as director of botanical medicine. This is the first position of its kind at a conventional medical school in the United States.

In 2002, the Federation of State Medical Boards of the United States responded to the increased interest in CAM by approving model guidelines for the use of complementary and alternative therapies in medical practice,10(Appendix E) which had been developed at its request. (These model guidelines are available at the Federation of State Medical Boards Web site, www.fsmb.org, under Policy Documents.) Recognizing that standards in evaluating health care practices must be consistent, whether considered conventional or CAM, the model guidelines provide a methodology for evaluating physician adherence to the state’s medical practice act and the following “do no harm” criteria. They question whether the physician is using a treatment that is

- effective and safe? Having adequate scientific evidence of efficacy and/or safety or greater safety than other established treatment models for the same condition.
- effective, but with some real or potential danger? Having evidence of efficacy, but also of adverse side effects.
- inadequately studied, but safe? Having insufficient evidence of clinical efficacy, but reasonable evidence to suggest relative safety.
- ineffective and dangerous? Proven to be ineffective or unsafe through controlled trials or documented evidence or as measured by a risk/benefit assessment.

The guidelines cover 7 aspects of patient care:

1. evaluation of patient
2. preparation of treatment plan
3. responsibilities during consultation and/or referral to other licensed health care provider
4. documentation of medical records
### TABLE 1: Coursework in Colleges of Pharmacy

<table>
<thead>
<tr>
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<tr>
<td><strong>Some coursework in</strong></td>
<td>Pharmacognosy</td>
<td>CAM</td>
<td>CAM</td>
</tr>
<tr>
<td><strong>Affirmative response</strong></td>
<td>74% (57/77)</td>
<td>72% (36/50)</td>
<td>73% (46/63)</td>
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<tr>
<td><strong>Average credit hours</strong></td>
<td>3</td>
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</tr>
</tbody>
</table>

Percentages refer to the number of colleges offering this instruction out of the total number of survey respondents.

* Includes 40 colleges of pharmacy teaching focused courses and 11 colleges of pharmacy offering miscellaneous lectures on natural products.

CAM = complementary and alternative medicine; N/A = not available.

### TABLE 2: Breakdown of Course Offerings by 64 Schools of Pharmacy in the United States

<table>
<thead>
<tr>
<th>Course Offerings</th>
<th>Required</th>
<th>Elective</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural product-focused</td>
<td>2</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>CAM/natural product-focused</td>
<td>3</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Miscellaneous lectures</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Schools without CAM/natural product offerings</td>
<td>–</td>
<td>–</td>
<td>13</td>
</tr>
</tbody>
</table>

CAM = complementary and alternative medicine.

5. documentation of medical knowledge with respect to methods offered
6. requirements for the sale of goods from physician offices
7. requirements for performing clinical investigations

### Roles for Pharmacists

Pharmacists have the motive, opportunity, and means to play key roles in caring for patients taking, or considering taking, herbal products and other types of alternative medicines. By actively assuming responsibility for counseling on appropriate use of botanicals and dietary supplements, pharmacists gain recognition as a source of expert information in this rapidly growing area and will contribute to improving the quality of care (motive). Compared with other members of the health care team, pharmacists have more frequent interactions with patients (opportunity) and a deeper understanding of how medicines work, alone and in combination with other agents (means).

A recent cross-sectional mail survey of 107 community pharmacists in Texas revealed that most (70%) knew of patients who had used CAM.24 These pharmacists reported that patients asked them about CAM, particularly in pharmacies that stock herbal and homeopathic preparations. Despite a belief that they need to know when patients are using CAM therapies—to respond to potential drug-botanical interactions, for example—these pharmacists rarely asked patients about CAM use and appeared to be reluctant to respond to inquiries about CAM.

These pharmacists had the opportunity and motive to be information resources about CAM. The patients asked questions, and the pharmacists knew it was important to have the CAM information to provide optimal care, but many of these pharmacists did not have the means to provide reliable information. The authors of the survey reported that pharmacists with access to evidence-based information on CAM were more likely to ask patients about CAM use and answer their questions.

In 2000, the American College of Clinical Pharmacy (ACCP) published a white paper on herbal products,25 proposing that the basis for pharmacist involvement with herbal products is an extension of their roles in pharmaceutical care and clinical pharmacy practice and their participation on collaborative health care teams. Unfortunately, formal education of pharmacy students about herbal and natural products—pharmacognosy, in general—has declined steadily since the 1970s. As recently as 1997, 20 of 77 pharmacy schools in the United States reported no instruction in herbal-botanical products in their curricula.26 Despite the increased use of these products, subsequent surveys have reported similar results, as shown in Table 1.27-29 Shields et al.21 also found that most formal instruction was offered in elective course work rather than in required pharmacy course work. Table 2 shows the courses offered in 64 schools of pharmacy.

In 2003, the National Association of Boards of Pharmacy began including questions regarding herbal products and nutraceuticals on the North American Pharmacist Licensure Examination. Perhaps this will provide further impetus for incorporating these topics into the pharmacy curriculum. Recent studies indicate medical and nursing schools are also adding CAM education to their curricula.30-32

Shields et al. did note an increase in the number of pharmacy schools offering courses devoted to CAM/natural products topics in the past 5 years, from 7 to 40.29 Rowell et al. report that increased offerings may be reflecting increased student interest in these topics.27 For example, a 3-credit phytomedicine course, offered as an elective to third-year PharmD students by the College of Pharmacy at the University of Arizona, experienced an increase in enrollment following integration of phytomedicine principles into core medicinal chemistry and pharmacotherapy courses.

ACCP suggested integrating core information on herbal and natural products across the curriculum into medicinal chemistry, pharmaceutics, and therapeutics. Furthermore, they stated that discussion of botanicals in therapeutics courses should (a) emphasize the findings and limitations of current research and the levels of evidence supporting or refuting their use and (b) suggest that botanicals and alternative therapies be held to the same efficacy, safety, and effectiveness standards as conventional treatments. Following this exposure, specific pharmacy course work could be designed to address other skills needed to...
prepare pharmacists for this additional responsibility: for example, the factors that motivate patients to use botanicals. ACCP outlined the following 4 core areas of focus for those involved in developing pharmacy curricula as well as for practicing pharmacists looking for continuing education in this subject area:

1. Pharmacists should have a thorough knowledge of the derivation, safety and efficacy, and drug interactions of common herbal and natural products.

2. All pharmacists should have the ability to triage individuals in an ambulatory environment to answer questions about herbal and dietary supplement products. However, the focus of these studies was whether a particular reference was able to answer a set of questions, not whether the information provided was accurate. That is, quantity was evaluated, not quality. There are very good reasons for this approach. Evaluating the accuracy of information in tertiary literature can be challenging, even more so when the subject is CAM. Chambliss et al. reviewed 52 books on botanical dietary supplements targeted to pharmacists and physicians, assessing their overall quality as primary and secondary references. Books judged to have high value provided primary references to support statements and included information necessary to assess the potential for drug interactions and safe use during pregnancy and lactation.

**CAM Examples in Community Pharmacy Practice**

Suppose, for example, a patient wants to know if chamomile tea in the evening will be helpful in initiating sleep. This patient has a history of blood clots and is taking an anticoagulant. A monograph on German chamomile in the Expanded Commission E Monographs reveals no documented interactions with other drugs; the tea is used as a mild sedative and sleep aid in Germany but Commission E did not grant approval for such use because of lack of published data. Nevertheless, one study that is referenced indicates that a water soluble component of chamomile, apigenin, binds at benzodiazepine receptor sites. So, there is a molecular basis for a weak central nervous system depressing effect, which could be researched further by requesting the cited reference.

Tyler’s Honest Herbal provides information regarding isolated reports of allergic reactions to chamomile, but no other words of caution.

This resource states that much of the value of chamomile lies in its volatile oil and that steeping the plant material for an extended time in a covered vessel extracts only about 10% to 15% of that volatile oil; however, when used over a long period, beneficial effects can accumulate. Mention is made of the presence of coumarins, in particular, herniarin and umbelliferone, which is of interest particularly if the patient is taking an anticoagulant. The only information given is that these substances contribute additional antispasmodic activity, along with other agents in the tea.

A 5-year-old copy of the Natural Medicines Comprehensive Database suggests that there is a theoretical possibility that large quantities of German chamomile interfere with anticoagulant therapy. Will the patient be drinking large quantities of chamomile? Recalling that “beneficial effects accumulate” leads to the hypothesis that this theoretical interference with anticoagulant therapy could increase over time. What is known about herniarin and umbelliferone? No mention is made of this theoretical interaction between anticoagulants and German chamomile in the more up-to-date online Natural Medicines Comprehensive Database. The reference for the interaction, found in the 5-year-old print material, is not included here, and, unlike the older print edition, the online database states that German chamomile may inhibit cytochrome P450 3A4 (CYP3A4) isoenzymes. Knowing that the anticoagulant the patient is taking is primarily a substrate of CYP2C8/9, what is the appropriate advice to give this patient? Is the chamomile available for purchase German chamomile? How much chamomile is in the tea bag or capsule? Does the manufacturer of the tea bag/capsule provide a principal component analysis of the chamomile to account for variability in chamomile species/subspecies? Perhaps it is safe for your patient to drink the chamomile infusion, but what about efficacy?

**Efficacy Versus Effectiveness Considerations**

Efficacy studies are performed under strictly controlled conditions that are carefully designed to reveal a difference in efficacy if a difference truly exists. The study patient population is typically defined narrowly, measurements are generally made under optimum conditions, and interpretation is highly controlled and well defined. The gold standard for efficacy studies is the randomized, placebo-controlled, double-blind clinical trial (RCT). The results of efficacy studies are offered as “proof of principle” in support of continuing studies such as effectiveness studies, which may explore the size of the effect in different study populations, at different clinical sites, and under different conditions of practice that are not as controlled as RCTs.

In essence, “efficacy” refers to whether well-controlled clinical trials show a treatment effect whereas “effectiveness” refers to whether the treatment effect transfers to real-world populations.
Viewed in terms of internal and external validity, “efficacy” has more to do with internal validity and “effectiveness” has more to do with external validity, i.e., generalizability. Botanical products present formidable challenges in designing efficacy and effectiveness studies because of a host of factors that include uncertainty of the true active ingredient and inconsistency in the formulation and quantity of ingredients in various sources of a given botanical product. Most of these products are not sufficiently characterized to test efficacy or predict that similarly prepared products would be effective in wider public use. Isolating the active agent(s) in botanicals and determining the mechanism of action(s) are essential first steps in their investigation.
via efficacy studies.

In its 2001 report, the IOM described an “effectiveness RCT,” taking the position that when evaluating treatments, “the results of a single well-designed outcomes study should be considered as compelling as the results of a single well-controlled randomized trial.”44 While the NCCAM committee chose not to recommend one particular hierarchy of evidence and concurs that, in general, an RCT is the preferred study design if the issue is establishing treatment efficacy, other study designs, including observational studies or effectiveness RCTs, may provide equally compelling evidence as that provided by an efficacy RCT.10(pp.97,88) CAM research is sometimes viewed as analogous to researching new surgical procedures. In both cases, there may be a long time lag between development, first use of a treatment, and the subsequent assembly of a body of scientific evidence of effectiveness.

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**Resources to Answer CAM Questions**

An understanding of pharmacology was necessary to answer the chamomile question, particularly when considering that the patient was taking another medicine. Comorbidities are common in patients, and this is one of the reasons it is critical for pharmacists to actively monitor the use of prescription medicines, botanicals, and dietary supplements. Decisions about the use of a specific treatment are highly dependent on understanding the pharmacology of other treatments already in place.

The process for finding, evaluating, and providing information, in general, is well documented in Drug Information, A Guide for Pharmacists.43 This text provides an extensive listing of resources beneficial for providing drug information related to both drug therapy and disease state management, including some specific to natural products that are included in Table 3.

Natural Standard,44 an international research collaboration founded by clinicians and researchers, aggregates and synthesizes data on CAM therapies. Information is incorporated into monographs based on a combination of evidence and consensus followed by blinded editorial and peer-review process. The monographs, designed to facilitate clinical decision making, are fully referenced to the primary literature with links to the abstracts available online. In addition to the databases, Natural Standard publishes monthly newsletters, reference books, research reports, and the Journal of Herbal Pharmacotherapy.

The American Botanical Council (ABC) is a nonprofit education and research organization dedicated to promoting the safe and effective use of medicinal plants and phytomedicines.45 As part of its ongoing mission to educate health care professionals about herbal medicine, ABC offers a 6 week internship program for PharmD students through the University of Texas at Austin, College of Pharmacy. ABC publishes its journal HerbalGram and provides a literature review service and continuing education materials to health care professionals. Information about these and other services provided by ABC is available at: www.herbgram.org.

Varro Tyler has said, “More misinformation regarding the efficacy of herbs is currently being placed before the consumer than at any previous time, including the turn-of-the-century heyday of patent medicines.”46 As documented in the NCCAM report, consumer interest and demand for herbal preparations and dietary supplements has increased dramatically. With the advent of increased accessibility to the Internet, consumers have more access to products and information. A 1997 study of Internet herbal information by students at the Albany College of Pharmacy compared claims made about 11 popular herbs with data from peer-reviewed journals and found that 45% of associated claims were true, 6% were false, and 2% were meaningless.47 The remaining 47% of claims were labeled as undetermined because no scientific evidence could be found to either support or refute the claim. Claims were also evaluated for substantiation either in the form of direct evidence on the Web site or references to supporting data, and only 36% of the Internet claims were substantiated; of these, only 40% could be verified as true.

An excellent guide to reliable herbal information on the Internet is The Herbal Internet Companion, by David Owen, education coordinator/librarian at the University of California, San Francisco and assistant clinical professor at the UCSF School of Pharmacy.48 Noting a lack of agreement among practitioners and researchers regarding authoritative resources on the use of herbals, educating health professionals and consumers to assess the quality of health-related information found on Web sites has become critically important. This small paperback book is essential in providing this education as well as categorizing and evaluating Web sites essential to providing up-to-date, reliable information to both consumers and health care professionals.

The NIH NCCAM home page has a “health information” link that will take the reader to a list of resources for finding evidence-based information on CAM therapies, including a link to free-of-charge searching for CAM articles on PubMed. A search for chamomile at the NCCAM Web site yielded a link to a clinical trial evaluating relaxation/guided imagery and chamomile tea in the treatment of functional abdominal pain in children. NCCAM has issued an evaluation of its accomplishments for the first 5 years along with a strategic plan for years 2005-2009. Complimentary copies can be ordered or downloaded from the NCCAM Web site.49

The NIH Office of Dietary Supplements maintains another excellent (and free) online resource.50 Clicking on the “health information” link will take the reader to a number of resources that can be used to formulate answers to patient questions about herbal and dietary supplements. The Journal of Natural Products, published jointly by the American Chemical Society and the American Society of Pharmacognosy, focuses on the chemistry and/or biochemistry of naturally occurring compounds or the biology of living systems these compounds...
are derived from. The United States Pharmacopoeia (USP) develops and distributes quality standards and information for medicine and health care delivery. The United States Pharmacopoeia-National Formulary (USP-NF), available online, contains standards for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements. Voluntary testing of the quality of ingredients used in dietary supplements is offered by USP, and a listing of supplements tested and where they are available is available online. USP offers educational courses, including a free dietary supplement education program available at the Web site, and operates 2 medication safety programs.

CAM Has Become Mainstream With Opportunities for Pharmacists

There is no doubt that use of CAM in the United States is widespread, with more than one third of adults in the United States reporting use of some form of CAM, total annual visits to CAM providers now exceeding visits to primary care providers, and annual out-of-pocket costs for CAM in excess of $27 billion. Friends share information about CAM remedies with each other, and television, the press, the Internet, and other media push CAM information to consumers. Hospitals already are offering, and managed care organizations are covering, some CAM therapies. Oxford Health Plans, now part of UnitedHealth Group, began offering a comprehensive CMA program 8 years ago, with a chronic pain management component for managed Medicare members that included massage therapy. Humana, in 2003, initiated a network of CAM providers—the American WholeHealth Network—providing a 30% discount to Humana members who use the network. Schools of medicine, nursing, and pharmacy are beginning to teach CAM subjects, particularly botanicals and dietary supplements.

NIH is actively promoting involvement of practitioners in investigating which CAM therapies show promise for incorporation into conventional or integrative medical practice. Pharmacists have an important role in the effective use of CAM therapies. Pharmacists are close to patients, with more contact hours than most other health care professionals. Pharmacists are motivated to be the experts on all drug interactions, including drug-herbal. Pharmacists are experts at finding information. Of course, finding information is only the first step to answering a patient’s question. Slawson and colleagues write, “Information is not knowledge. Knowledge comes from the interpretation of information. While we are constantly bombarded with data and information, what we want is knowledge and wisdom, i.e., the ability to understand and apply the facts.”

All pharmacists have a role in the effective use of CAM therapies. Individual pharmacists can have an effect on the quality of patient care in CAM therapy by assessing the information that is available on relevant Web sites or becoming involved in the government-sponsored organizations mentioned in this article. Community pharmacists and managed care pharmacists can investigate the services available at the integrative medicine centers in local service areas. Managed care pharmacists can also organize or participate in CAM subcommittees of P&T committees.

DISCLOSURES

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A Review of the Use of CAM Therapy and the Sources of Accurate and Reliable Information

In Search of Safe and Effective Oral Anticoagulation

There is a large gap between the need for anticoagulation and the use of drug therapy for this purpose in ambulatory care. Major lower-extremity orthopedic surgery such as total hip replacement and total knee replacement are associated with an increased risk of venous thromboembolism (VTE). Anticoagulant prophylaxis is necessary to reduce the risk of deep vein thrombosis (DVT), which may progress to symptomatic outcomes such as pulmonary embolism (PE). Prophylaxis and treatment of patients with symptomatic VTE occurs in 2 phases. Initial therapy focuses on rapid achievement of effective anticoagulation and usually involves subcutaneous low-molecular-weight heparin. Long-term prophylaxis, with the vitamin K antagonist, warfarin, reduces the risk of recurrent VTE from about 27% (without prophylaxis or inadequate prophylaxis) to 4% during the first 3 months of observation.

While warfarin is a marvelous, life-saving drug, the safety risk from bleeding, need for continuous monitoring, and interaction with many common drugs limit its more widespread and long-term use. The search for a suitable alternative that would provide similar efficacy in anticoagulation with lower risk of bleeding has centered on ximelagatran (Exanta) in recent years, an oral direct thrombin inhibitor (DTI). However, large expectations for an alternative to warfarin therapy with ximelagatran were dashed on September 10, 2004, when a U.S. Food and Drug Administration (FDA) advisory panel declined to recommend approval of ximelagatran because of safety concerns. After 3 months of therapy with ximelagatran, 546 (7.9%) patients had an alanine aminotransferase (ALT) value more than 3 times the upper limit of normal versus 1.2% for comparators. The panel also expressed concern over the apparent 3-fold increased risk of heart attacks in short-term use in knee-surgery patients. At the time of the FDA advisory panel decision more than a year ago, ximelagatran was approved for use in Europe for short-term therapy (12 days) in knee surgery patients.

Atrial fibrillation (AF) is the most common dysrhythmia seen by clinicians, and it commonly requires anticoagulation therapy for primary prevention of strokes or other embolic events. Decision analysis in the treatment guidelines for AF from the Agency for Healthcare Research and Quality (AHRQ) indicated that aspirin is the most cost-effective therapy for patients at low risk of stroke (approximately 1% per year), and warfarin was determined to be the most cost effective when the risk of stroke was judged to be high (10% or higher per year). For patients at intermediate risk (3% to 6% per year) of ischemic stroke, the choice between aspirin and warfarin is less clear and depends on the assumption regarding quality of life on warfarin versus aspirin therapy. Overall, for every 1,000 patients with AF who are treated with warfarin for 1 year, 30 strokes are prevented at the expense of 6 major bleeds.

In a cohort study of 11,526 adult members of the Kaiser health system in northern California with nonvalvular AF over 12,958 person-years of warfarin exposure, there were 148 incident thromboembolic events (141 ischemic strokes, 7 other thromboembolism) for warfarin therapy (1.17 per 100 person-years, 95% confidence interval [CI], 1.00-1.38) versus 249 events (231 ischemic strokes, 18 other thromboembolism) among patients not receiving warfarin (2.03 per 100 person-years, 95% CI, 1.79-2.30; P < 0.001). After adjusting for potential confounders and the likelihood of receiving warfarin using proportional hazards models, warfarin therapy was associated with a 51% (adjusted hazard ratio [HR], 0.49; 95% CI, 0.40-0.61) lower risk of thromboembolism compared with no warfarin therapy (either no antithrombotic therapy or aspirin). Warfarin was also associated with a reduced risk of all-cause mortality (adjusted HR, 0.69; 95% CI, 0.61-0.77). While the incidence of intracranial hemorrhage was rare, patients taking warfarin did have a higher rate (0.96 per 100 person-years vs. 0.23 per 100 person-years for those not taking warfarin, P=0.003; adjusted HR, 1.97; 95% CI, 1.24-3.13) but there was no increased risk of nonintracranial hemorrhage.

The length of anticoagulant therapy is nearly as important as the intensity of anticoagulation in the prevention of recurrent VTE. In a meta-analysis of RCTs with results published from 1969 through 2004 in PubMed, EmBase Pharmacology, the Cochrane database, clinical trial Web sites, and a hand search of reference lists, Ost et al. determined that the incidence of recurrent VTE with long-term (>6 months) anticoagulation therapy in patients with a first episode of VTE (or therapy that involved anticoagulation with one or more agents) was 0.020...
events per person-year (i.e., 1 in 50) compared with a rate 6 times higher (0.126 events per person-year) for shorter therapy (P<0.001). The authors concluded that the optimum length of warfarin therapy was not clear, but 6 or more months of treatment appeared to be beneficial, particularly for patients at higher risk, even though the duration of anticoagulation beyond 6 months results in a relatively modest incremental risk reduction. What is more, this study pointed out that (a) the number needed to treat to prevent 1 VTE event with long-term anticoagulation would be approximately 50 (95% CI, 25-1,000), (b) the effect size with lifelong therapy is much larger since the number needed to treat to prevent 1 VTE event with lifelong anticoagulation would be approximately 9 (95% CI, 7-14), but (c) the relative amount of harm that is associated with each adverse outcome is important to consider since, for example, the damage from an intracranial hemorrhage can be much more serious than a VTE of the lower extremity. During therapy with vitamin K antagonists, the risk of recurrence is very effectively reduced—by approximately 90%—to 0.7 episodes per 100 person-years. In the 6 to 12 months immediately after the discontinuation of therapy, a catch-up phenomenon occurs, resulting in an absolute incidence of recurrence of VTE of 5% to 10%. This phenomenon has been observed after 3, 6, and 12 months of vitamin K antagonist therapy and, therefore, suggests that prolonging this therapy delays recurrence until the therapy is stopped, rather than reducing the risk of recurrence except in patients at high risk of recurrent VTE. During the subsequent years, the risk of recurrence stabilizes, and the annual incidence of recurrence is 1% to 2%. The American Heart Association estimates that about 15% of all strokes in the United States occur in people with AF and analysis of medical therapy of AF; using data from the National Ambulatory Medical Care Survey (NAMCS), showed that fewer than half of AF patients at risk for stroke received anticoagulation therapy in the United States from 1991 through 2000. While the NAMCS data were encouraging in the United States from 1991 through 1992 to 41% in 1999-2000 (P<0.001). Only 46.5% of patients at high risk of stroke received warfarin and 20.6% received neither aspirin nor warfarin; (b) only 75.5% of patients with acute myocardial infarction received aspirin on arrival at the hospital and only 85.6% received prophylaxis with either a parenteral anticoagulant or oral warfarin; (c) in 49.4% of patients with DVT, PE, or both who received unfractionated or low-molecular-weight heparin, the anticoagulation therapy was discontinued before an INR of 2.0 or greater was achieved for 2 consecutive days; and (d) patients with DVT or PE were rarely discharged from the hospital with bridge therapy (an injectable anticoagulant agent plus warfarin), although the length of hospitalization was significantly shorter for injectable anticoagulant plus warfarin compared with discharge with warfarin alone (4.0 vs. 8.1 days, P<0.001).

Maximization of the market opportunity for a warfarin replacement will, at some point, involve consideration of the economic consequences and opportunities associated with recurrent VTE events. In this issue of JMCP, the manufacturer of ximelagatran sponsored research reported by Bullano et al regarding direct hospital and medical costs associated with recurrent VTEs, obtained from examination of administrative claims data from a managed care organization (MCO) composed of approximately 11 million members. A cohort of 2,147 patients was identified by an incident in-hospital VTE event consisting of DVT, PE, or both DVT + PE, indicating a prevalence of 2.04 VTE patients per 100,000 MCO members. The average cost per recurrent VTE event that required rehospitalization was $14,975. During the postindex period, a total of 612 of the 2,147 patients experienced an average of 2.43 bleed events that did not require hospitalization, at a mean cost of $239 per event.

A few other points are notable in the study by Bullano et al. VTE was not necessarily the principal index diagnosis; i.e., these VTE patients could have been admitted for any principal diagnosis at the index hospitalization. The claims were for sick patients, including 59.2% with a history of or active malignancy, 24.5% with a coincident diagnosis of trauma, and 22.9% with a coincident diagnosis of AF. Of the 26,103 VTE patients identified initially, 13,703 (57% of the 23,956 excluded patients) were excluded for not having at least 1 pharmacy claim for an anticoagulant after hospital discharge. Warfarin treatment following the incident VTE event was administered to 97.3% of patients, for an average of 6.7 (median 5.0) months, but the standard deviation was 6 months, and warfarin therapy was defined by as little as 1 pharmacy claim. The cost of warfarin drug therapy was low, just $19.40 per patient per month. In the nearly 2 years of average follow-up, 534 (24.9%) experienced an average of 1.24 bleed or recurrent VTE events that required hospitalization. Stated another way, the average cost of hospitalization for recurrent VTE or bleed events was $3,729 over nearly 2 years of follow-up (or $2,101 per patient per year) for these patients with an index VTE event during a prior hospitalization for any reason.

Among the several limitations of the study by Bullano et al. was the absence of data regarding the availability and use of anticoagulation management services for these MCO members. We do not know how many of the 534 patients with a recurrent VTE event did not receive care from an anticoagulation...
management service. We also do not know the INR laboratory values for any of these patients during follow-up or when the recurrent VTE event occurred relative to discontinuation of warfarin (or other antithrombotic) therapy. Left to other researchers is investigation of the relationship of recurrent VTE cost to the length and intensity of warfarin anticoagulant therapy and the magnitude of the effect of an anticoagulation management service on clinical and cost outcomes in these patients.

The sponsor of the research reported by Bullano et al. is the manufacturer of ximelagatran, and 2 of the coauthors are employees of the manufacturer. All of the clinical trial results for ximelagatran reported thus far in the medical literature have been sponsored by the manufacturer, including SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) III, an open-label trial conducted in Europe. Among 3,407 high-risk patients with AF over a mean length of 17 months of follow-up, ximelagatran had an incidence of 40 strokes (1.6% per year) or embolic events compared with 56 strokes among warfarin patients (2.3% per year); absolute risk reduction 0.7% (95% CI, -0.1 to 1.4); P = 0.10.29 More warfarin patients (86%) completed the study than did ximelagatran patients (82%), and the total mortality was approximately the same in both groups (4.6%). The rate of secondary events in each group was similar, with the exception of bleeding complications, which occurred in 25.8% of patients per year in the ximelagatran group versus 29.8% in the warfarin group; relative risk reduction 14% (95% CI, 4-22); P = 0.007. However, the ximelagatran patients were far more likely (6.1% vs. 0.8% for warfarin) to experience ALT levels at least 3 times the upper limit of normal within the first 6 months of the trial.4 In the ESTEEM (Efficiency and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage) trial, elevation of ALT serum levels to more than 3 times the upper limit of normal within the first 6 months of the trial occurred in 11% of ximelagatran patients treated for 6 months versus 2% for placebo.19

In SPORTIF V, 3,922 AF patients with at least 1 stroke risk factor at 409 North American sites were randomized to receive adjusted-dose warfarin (target INR 2.0 to 3.0) or fixed-dose oral ximelagatran (36 mg twice daily).20 The primary event rates (ischemic and hemorrhagic strokes and systemic embolic events) over an average 20 months of follow-up were 1.2% per year in the warfarin group and 1.6% per year in the ximelagatran group, an absolute difference of 0.45% per year (95% CI, -0.13 to 1.03; P < 0.001). When all-cause mortality was included with the primary events, the rate difference between groups by intent to treat was 0.10% per year (95% CI, -0.97 to 1.18; P = 0.86). Rates of disabling or fatal stroke, hemorrhagic stroke, and major bleeding did not differ significantly between groups, but serum ALT levels rose transiently above 3 times the upper limit of normal in 6.0% of patients on ximelagatran versus 0.8% of patients on warfarin (P < 0.001) within the first 6 months of treatment.

In 2003, the year before the FDA decision to not approve ximelagatran for use in the United States, the medical literature was already peppered with observers almost giddy over the expectant demise of anticoagulation clinics engaged in warfarin monitoring and management.21,22 Just a few months later, in early 2004, there was increased recognition that, while the occurrence of major bleeding seems lower with ximelagatran, it is necessary to treat 167 patients with ximelagatran to prevent 1 major bleeding event per year compared with warfarin, but the number needed to harm (for increased concentration of liver enzymes) is 19 patients on ximelagatran.23

The clinical trials of ximelagatran, all sponsored by the manufacturer, have generally found (a) comparable efficacy to enoxaparin and warfarin but (b) elevated liver enzymes and a possible increased risk of myocardial ischemia. In a randomized double-blind trial with concealed allocation (level of evidence = 1b)24 of 2,489 patients with acute DVT, including one third with PE, Fiesinger et al. found 36 mg of ximelagatran twice daily for 6 months was comparable to enoxaparin 1 mg per kg twice daily for 5 to 20 days followed by warfarin adjusted to an INR range of 2.0 to 3.0.25 The THRIVE (Thrombin Inhibitor in Venous Thromboembolism) Treatment Study reported by Fiesinger et al. found an incidence of 2.1% recurrent DVT in the ximelagatran patients versus 2.0% in the enoxaparin/warfarin patients (an insignificant absolute difference of 0.2%), but the ximelagatran patients were more likely to have increased levels of ALT more than 3 times the upper limit of normal (9.6% vs. 2.0%). Symptomatic myocardial ischemia leading to hospitalization was noted in 10 patients (0.8%) treated with ximelagatran versus 1 patient treated with enoxaparin/warfarin (0.08%) (P = 0.006).

EXULTA (Exanta Used to Lessen Thrombosis A) was a randomized, double-blind trial involving 1,851 patients undergoing total knee replacement. EXULTA compared a regimen of 7 to 12 days of oral ximelagatran, at a dose of 24 or 36 mg twice daily, starting the morning after surgery, with warfarin therapy started the evening of the day of surgery.26 For the primary outcome measures (composite end point of venous thromboembolism and death from all causes), ximelagatran appeared superior to warfarin, (20.3% vs. 27.6%; P = 0.003), and major bleeding was not different, 0.8% for ximelagatran versus 0.7% for warfarin. For the composite secondary end point, proximal DVT, PE, or death, the difference was also not significant (2.7% for ximelagatran vs. 4.1% for warfarin; P = 0.17). Criticism followed publication of the EXULTA trial, including the point that the apparent small superiority of ximelagatran over warfarin could have been predicted from the study design and the slower onset of action of warfarin since the therapeutic INR range had not been reached in 35% of the patients in the warfarin group by postoperative day 3 and in 24% of the patients in this group by the day of venography.27

Experts have leveled additional criticism at the study designs in clinical trials that have alleged value of ximelagatran. For example, Schulman et al., in a double-blind, multicenter...
trial (THRIVE III) of 1,233 patients with VTE, found ximelagatran superior to placebo in preventing recurrent VTEs over an 18-month follow-up period. All patients had received 6 months of anticoagulant therapy followed by an average of 18 months of secondary prevention with either ximelagatran 24 mg twice daily or placebo. The occurrence of the primary end point, symptomatic recurrent VTE, was confirmed in 12 of 612 patients assigned to ximelagatran (2.0%) versus 71 of 611 patients (11.6%) assigned to placebo (HR, 0.16; 95% CI, 0.09-0.30; P < 0.001). Death from any cause occurred in 2004;164(1):55-60.

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initiation of prophylaxis of VTE, and 1 each for initial treatment of VTE, including 5 for post-

placebo group, and bleeding occurred in 134 patients in the ximelagatran group versus 111 patients in the placebo group (HR, 1.19; 95% CI, 0.93-1.53; P = 0.17). The incidence of major hemorrhage was low (6 events in the ximelagatran group and 5 in the placebo group), and none of these hemorrhages were fatal. The cumulative risk of a transient elevation of the ALT level to more than 3 times the upper limit of normal was 6.4% in the ximelagatran group compared with 1.2% in the placebo group (P < 0.001). Boger et al. criticized the Schulman study for inclusion of a large number (129) of high-risk patients in the placebo group, citing the increased risk of recurrent VTE after an episode of VTE in patients with cancer or known recurrent VTE, which can be reduced by prolonged anticoagulation. Vakman et al. complained about the 97 patients (16%) in the placebo group who had a history of recurrent VTE of up to 4 events each.60

There have been at least 10 large controlled, clinical trials of DTIs in prophylaxis of treatment of VTE, including 5 for post-operative initiation of prophylaxis of VTE, and 3 for preoperative initiation of prophylaxis of VTE, and 1 each for initial treatment of acute VTE and long-term secondary prophylaxis of VTE. Nevertheless, (a) there are few indications for DTIs and (b) the DTIs have demonstrated comparable but not superior efficacy, with similar safety, to heparin, enoxaparin, or warfarin. While 4 parenteral DTIs have been approved by the FDA, ximelagatran is the only oral DTI that has shown promise in AF. Nevertheless, (a) there are few indications for DTIs and (b) the DTIs have demonstrated comparable but not superior efficacy, with similar safety, to heparin, enoxaparin, or warfarin. While 4 parenteral DTIs have been approved by the FDA, ximelagatran is the only oral DTI that has shown promise in AF. Unfortunately, ximelagatran is tripped up by concern regarding hepatotoxicity. Therefore, the search continues for safe and effective oral anticoagulation, and the pharmacist specialists and other clinicians involved in warfarin management services do not appear to be in immediate danger of unemployment.

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REFERENCES


**Letters to the Editor**

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