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Make “vroom” for Charles Maher! This prominent automotive artist was pleasantly surprised to hear that the editors of a nonautomotive publication such as JMCP wanted to use his Packard in the Fall painting for their October cover. Maher has done paintings for the covers of such magazines as AutoWeek, Sports Car Market, and Automobile Quarterly. His art has also appeared on the pages of Racer, Car Collector, Road & Track, Automobile, and Mustang Monthly magazines. Maher is a past president of the National Automotive Artists Association and a long-time member of the Automotive Fine Art Society (AFAS). His work can be found in the book, A Celebration of Automotive Art, written by Gerry Durnell and the staff of Automobile Quarterly. It is a splendid compendium of fine art created by artists of the AFAS.

Maher was born in Kansas City, Missouri, and grew up in Miami, Florida. He first became interested in art when he was in the eighth grade. “I enjoyed drawing weird things in school to make my friends laugh. Mad was my favorite magazine, and I liked the work of Don Martin, one of Mad’s most famous artists,” he said. “Another early influence was my mom—she used to paint watercolors and oils of landscapes and flowers.” Although Maher had artistic aspirations as a teenager in the early 1960s, it turned out that he would have to wait awhile to channel his creative energy. He enrolled at the University of Notre Dame as a premed student, but struggled with his chemistry studies during his freshman year. Maher decided to seek the advice of a school guidance counselor. “Fortunately for Charlie, and for us, he found a mentor who recognized the symptoms of a stifled artist and steered the young man into the fine arts program, with an industrial design concentration,” wrote Kevin A. Wilson, executive editor of AutoWeek. Maher graduated with a bachelor’s degree in fine art.

He learned to drive at the wheel of his family’s ‘55 Chevy Bel Air, and a few years later, he drove their 1960 Chrysler 300. But the “car bug” didn’t really bite Maher until he started going to car races with a friend. In 1968, his passion for cars and art came together when he was hired by the Ford Motor Company as a designer. Maher spent eight years with Ford before moving on to a Detroit graphics firm that dealt with quite a few automotive companies. He assisted in the design of production car graphics for Ford, General Motors, and Toyota. Other projects included the creation of pace car graphics for Indianapolis Motor Speedway and Long Beach Grand Prix.

Throughout Maher’s years as a designer, he was painting just for his own pleasure and taking advantage of opportunities to visit galleries in New York, Chicago, London, Brussels, Amsterdam, Venice, and Florence. In 1988, he shifted gears and set out on his own as an artist, illustrator, and designer.

When asked what inspired him to paint Packard in the Fall, Maher replied, “I was going to do a series of four paintings depicting the four seasons. This one in the fall (and a summer piece) are the only two that I ever completed. I wanted to show a car that was a classic, and the color of this particular Packard was one that I felt would be complementary to the brilliance of the fall colors. Originally, there was no figure in the painting, but I thought it could use one—hence the woman, who has stopped to pick flowers.” The magnificent Packard is a 1934 V-12 LeBaron-bodied, dual cowl, Phaeton. Maher painted the convertible in greater detail than the background trees and figure, making it the undeniable focus of the picture. His style has evolved over the years, becoming looser. “Experience is a great teacher,” he remarked. Maher works almost exclusively in acrylics, and he tends to vary his technique from painting to painting. Besides using traditional brushstrokes, he may apply the paint with a palette knife, squeeze it straight from the tube onto the canvas, or step back and splatter an area with color.

Maher’s home-based studio is located in Bloomfield Hills, Michigan; his fabulous artwork can be seen on his Web site: www.doctor-design.com/maherautoart. He is represented by New Masters Gallery in Carmel, California, and Automotive Emporium Gallery in Dallas, Texas. His paintings have been displayed at Concours d’Elegance classic car expositions across the country, and he has had two separate one-man shows at the Automotive Hall of Fame Museum in Dearborn, Michigan. Maher has also created numerous posters for various automotive events in Michigan. He is currently working on his eighth consecutive poster for the annual Woodward Avenue Dream Cruise in Ferndale, Michigan.

In addition to attending a variety of car exhibitions throughout the year, Maher likes to go to auto races at venues such as Daytona, Sebring, Indianapolis, Road Atlanta, and Laguna Seca. He enjoys getting as close to the action as possible—you might even see him in his fire suit, shooting photos in the pit.

Sheila Macho
Cover Editor

COVERAGE CREDIT
Charles Maher, Packard in the Fall, acrylic on canvas, Bloomfield Hills, Michigan. Copyright© 1994.

SOURCE
Interview with the artist.
Administrative Claims Analysis of the Relationship Between Warfarin Use and Risk of Hemorrhage Including Drug-Drug and Drug-Disease Interactions

KUI ZHANG, MD; CHRISTOPHER YOUNG, PhD; and JAN BERGER, MD

ABSTRACT

BACKGROUND: Despite the risk of hemorrhage, warfarin is the most commonly used oral anticoagulant today, both as monotherapy and when taken in combination with selected drugs. Warfarin is used most commonly for irregular heartbeat, after a heart attack, and after joint or heart valve replacement surgery.

OBJECTIVE: To evaluate the relative risk of hemorrhage in health plan members who received warfarin concomitantly with a drug known to cause an interaction or after diagnosis of liver disease or heart failure (HF).

METHODS: A cohort study sample was drawn from an administrative database comprising medical and pharmacy claims for 1.7 million health plan members. A health plan member was defined as anyone who was eligible for pharmacy and medical benefits at any time from October 1, 2003, to September 30, 2004. To be included in the study, a member must have received at least 1 pharmacy claim for warfarin during the study period and been younger than 100 years. Hemorrhage was defined as a diagnosed bleeding episode recorded on a medical claim within 7 calendar days of a fill date for a pharmacy claim (new or refill) for warfarin. The following variables were used to predict the outcome measures: type of drug-drug or drug-disease interaction, patient age and gender, number of unique prescribers during the year for all drugs, specialty of the first prescriber for warfarin, average dose of warfarin, and days of warfarin therapy. Because individuals were followed only during the calendar year under study, the authors have interpreted the days of therapy measured primarily as a control on exposure. The outcome measures are prevalence of drug and disease interactions among members receiving warfarin therapy and the per-patient-per-year and per-member-per-month (PMPM) cost of medical treatment of hemorrhage associated with warfarin therapy including drug and disease interactions. Costs are defined as the total paid amount for a procedure or service after negotiated provider discounts and subtraction of patient copay and deductibles. Logistic regression was used to evaluate the relative risk of hemorrhage in users of warfarin monotherapy and of warfarin users with drug-drug and drug-disease interactions. The comparison group in the logistic regression comprised the members who were not diagnosed with either HF or liver disease and who received warfarin therapy but none of the drugs under study known to cause drug interactions. Therefore, the odds ratios (ORs) produced were estimates of the relative risk of hemorrhage when taking warfarin concomitantly with selected drugs and diseases.

RESULTS: Of the 17,895 patients who used warfarin during the study year, 2,634 (14.7%) were diagnosed with a hemorrhage event within 1 week after filling a prescription for warfarin. The factors associated with an increased risk of hemorrhage included female gender (OR 1.149; 95% confidence interval [CI], 1.053-1.253), liver disease (OR 1.764; 95% CI, 1.360-2.288), and HF (OR 1.559; 95% CI, 1.373-1.770). Compared with the use of warfarin alone, the use of either cephalosporins (OR 1.157; 95% CI, 1.043-1.285) or metronidazole (OR 1.578; 95% CI, 1.321-1.886) was associated with increased risk of hemorrhage, whereas the risk of hemorrhage was not greater for concomitant use of warfarin with amiodarone, fibrin acid derivatives, or nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors. There was no relationship between estimated average daily warfarin dose and prevalence of hemorrhage. Other variables associated with an increased risk of hemorrhage were increased patient age, female gender, 120 days or more of warfarin therapy during the year, 2 or more unique prescriber numbers, and the medical specialty of the first prescriber of warfarin. Over the population of 1.7 million members, the cost for all hemorrhage events within 7 days of a pharmacy claim for warfarin was $0.40 PMPM.

CONCLUSIONS: Only 2 of 5 combinations of warfarin with drugs in this study were found to be associated with a higher prevalence of hemorrhage compared with warfarin use alone. The absolute prevalence of hemorrhage in users of warfarin and metronidazole was 22.7% and 17.2% for warfarin and cephalosporins, respectively, versus 14.2% in users of warfarin alone. The prevalence of hemorrhage for concomitant use of warfarin and NSAIDs/COX-2 inhibitors, amiodarone, or fibrin acid derivatives such as fenofibrate was not greater than for warfarin alone. Liver disease or HF in warfarin users was associated with a significant increase in the likelihood of hemorrhage.

KEYWORDS: Patient safety, Warfarin

J Manag Care Pharm. 2006;12(8):640-48

RESEARCH

Research on medical errors has highlighted the prevalence of potential treatment-caused injuries in the United States. These medical errors can include drug-drug and drug-disease interactions. These interactions can result from proximal causes such as inattention by practitioners, lack of prescriber knowledge regarding the drugs, and lack of knowledge regarding the patient’s drug history when drugs that interact are prescribed. Often, system errors such as defects in drug or patient knowledge dissemination can be identified that lead to these proximal causes.

Warfarin, a medication that inhibits the synthesis of clotting factors, is the most commonly used oral anticoagulant today. Warfarin acts by interfering with hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X). Physicians use warfarin for the treatment and prevention of venous thromboembolic disorders and the prevention of thromboembolic complications in patients with atrial fibrillation, valvular heart disease, mechanical and bioprosthetic heart valves, and implanted artificial joints.

Risks are associated with the use of warfarin, however. The main hazard associated with warfarin therapy is the risk of

Note: An editorial on the subject of this article appears on pages 686-87 of this issue.

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hemorrhage. Hemorrhage is a concern for warfarin monotherapy and for warfarin used concomitant with other drugs and in the presence of certain diseases. Of particular concern are warfarin users with heart failure (HF) who subsequently suffer from hepatic dysfunction and are at increased risk of hemorrhage. Gurwitz et al. found that hemorrhage is the most common type of preventable adverse drug event among older persons in an ambulatory clinical setting. Landefeld and Beyth found that the average annual frequencies of fatal, major, and major or minor bleeding during warfarin therapy were 0.6%, 3.0%, and 9.6%, respectively. These frequencies are approximately 5 times those expected without warfarin therapy. Individuals who use warfarin either concomitantly or with the use of other drugs, such as mifepristone, antithrombotic medications, aspirin, certain fibric acid derivatives, or metromidazole, who are diagnosed with certain conditions, including liver disease, active bleeding, recent trauma, or blood dyscrasias, are at increased risk of hemorrhage.

While the potential dangers of warfarin drug-drug and drug-disease interactions and the prevalence of concomitant use of warfarin with drugs that may result in a drug-drug and drug-disease interaction are known, less is known about the prevalence of clinical consequences and the cost of these drug-drug and drug-disease interactions. Evidence of clinical and economic consequences of drug-drug and drug-disease interactions may help quantify the need for additional education and/or other interventions. In this study, we used administrative medical and pharmacy claims data to evaluate the relative risk of hemorrhage in individuals taking warfarin concomitantly with other drug therapy known to be associated with drug interactions or with diagnosed liver disease, compared with the use of warfarin alone. The working hypothesis of this study is that patients using warfarin concomitantly with selected drugs and diseases (see Methods) have a greater relative risk of hemorrhage than do patients taking warfarin alone.

### Methods

This analysis was conducted from the perspectives of the health plan and payer to provide information on the incidence of drug-drug and drug-disease interactions and of related adverse events. In this way, the information created in this study focuses not on the member's risk of hemorrhage but on the overall clinical and economic costs that a health plan payer bears as a consequence of drug-drug and drug-disease interaction. Benefits eligibility, which ensures that all information for a study subject is available for examination, does not allow for estimates of overall incidence of drug-drug and drug-disease interactions in a population. In an eligibility-controlled analysis, members without a full year of eligibility because of death or termination of benefits or for some other reason would be dropped from the analysis.

Therefore, rather than conducting a retrospective longitudinal analysis of individuals, tracking their use of medications after their first diagnosis of hemorrhage, we chose to analyze 1 calendar year of administrative claims data. This cohort study sample of combined deidentified medical and pharmacy claims data was drawn from 1.7 million health plan members for whom both medical and prescription data were available to Caremark Rx, a pharmacy benefits manager (PBM). This PBM provides services to a subset of these plans that require the health plans to provide medical claims data. The database of pharmacy and medical claims represented approximately 1.7 million individuals who were eligible for pharmacy and medical benefits at some time during the period under study (October 1, 2003, to September 30, 2004). To be included in the study, an individual must have been a member of a health plan that provided both medical and pharmacy claims data, must have received at least 1 pharmacy claim for warfarin during the study period, and must have been younger than 100 years. Table 1 describes the selection of the final study sample of 17,895 members who used warfarin during the year.

We followed 3 sets of events over time in this analysis: (1) the receipt of 2 pharmaceuticals or a pharmaceutical and a diagnosis that might result in a drug-drug or drug-disease interaction, (2) the diagnosis of hemorrhage within 1 week after the drug-drug or drug-disease interaction, and (3) the paid (plan) costs of hemorrhage that occurred after the drug-drug or drug-disease interaction through the end of the calendar year. Detailed definitions and descriptions of the selection process for drugs and diseases under study and of each of these outcomes follow below.

The primary source we used to identify potential warfarin-drug and warfarin-disease interactions was the book Pharmacology. From this volume, we obtained a list of warfarin interactions from the section on warfarin (pp. 321, 322). To supplement this source, we used computer searches of medscape.com and google.com of the phrase “interactions of warfarin with drugs.” From this list, we considered for study drugs that potentiate the anticoagulant effect of warfarin and that have one of the following characteristics: (1) inhibit hepatic drug metabolism (cimetidine, imipramine, co-trimoxazole, chloramphenicol, ciprofloxacin, metronidazole, and amiodarone);
Of those conditions, HF and liver disease occurred often enough in the study population to allow the use of statistical methods to evaluate the risk of hemorrhage.

We considered 3 medical conditions for analysis: liver disease, HF, and thyrotoxicosis. Of those conditions, HF and liver disease occurred often enough in the study population to allow the use of statistical methods to evaluate the risk of hemorrhage.

Using these clinical and empirical criteria, warfarin users with a potential drug-drug and drug-disease interaction were identified and grouped for study using the following criteria: a diagnosis of liver disease (International Classification of Diseases, Ninth Revision, Clinical Modification, [ICD-9-CM] of 570.xx, 571.xx, 572.xx, or 573.xx) or HF (ICD-9-CM) of 428.0, 428.22, 428.23, 428.32, 428.33, 428.42, or 428.43) or who received a pharmacy claim for one of the following drugs or drug classes: NSAIDs (including cyclooxygenase-2 [COX-2] inhibitors), metronidazole, amiodarone, cephalosporins, and fibric acid derivatives.

A member with a potential drug-drug interaction was defined as an individual who had pharmacy claims in the database for 1 of these drugs and warfarin with at least 1 day of overlap in days supply of the 2 drugs. Members were not differentiated on the basis of the number of days of overlap. A member with a potential drug-disease interaction was defined as a member recently diagnosed with liver disease or HF. The criterion was selected arbitrarily as the presence of a diagnosis code within 3 weeks before a member filled a warfarin pharmacy claim. Hemorrhage was defined as the presence of a diagnosis code (Table 2) on a medical or hospital claim for a member who received a warfarin fill in the previous 7 calendar days. As noted in the footnote to Table 3, individuals who received warfarin through mail order would have a smaller number of “windows” during which we would count hemorrhaging. Following a conservative approach to estimation, we have not attempted to account for this difference by adding days to mail-order claims. Therefore, the cohort was defined as the group of individuals with a potential drug-drug and drug-disease interaction who, within 7 calendar days, experienced hemorrhage. This episode of hemorrhage was assumed to be related to the drug-drug and drug-disease interaction.

We evaluated the rate of hemorrhage in a comparison group of individuals who received warfarin therapy but no interacting pharmaceutical therapy or medical condition. The relative risk of hemorrhage was evaluated by comparing the rate of hemorrhage of individuals who received warfarin therapy but no interacting drug or medical condition. The relative risk of hemorrhage was evaluated by comparing the rate of hemorrhage of individuals who received warfarin therapy but no interacting drug or medical condition.

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Direct medical costs were estimated using the total amount paid for a procedure or service after negotiated provider discounts and subtraction of patient copayment and deductibles for all records with a diagnosis of hemorrhage subsequent to the first instance of a drug-drug and drug-disease interaction. Included in these costs are inpatient hospital stays, outpatient hospital visits, emergency room visits, and lab tests. We did not

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<td>360.43</td>
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<td>363.72</td>
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<td>372.72</td>
<td>374.81</td>
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<td>459.0x</td>
</tr>
<tr>
<td>531.0x</td>
<td>531.2x</td>
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<td>533.6x</td>
</tr>
<tr>
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<td>535.0x</td>
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<td>719.15</td>
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<td>719.19</td>
<td>722.4x</td>
</tr>
<tr>
<td>786.3x</td>
<td>958.2x</td>
</tr>
</tbody>
</table>

Administrative Claims Analysis of the Relationship Between Warfarin Use and Risk of Hemorrhage Including Drug-Drug and Drug-Disease Interactions

attempt to weight costs based on the placement of the ICD-9-CM code in the primary, secondary, or tertiary claim fields on the medical or hospital claim. However, only costs for medical and hospital claims with an ICD-9-CM code for hemorrhage were used. Costs to the health plans were calculated in 2 ways. One, per-member-per-month (PMPM) costs were defined as total dollars paid for claims for warfarin users with a diagnosis of hemorrhage divided by an estimated average member-month count (the total number of 1,701,724 members in the health plan during that year multiplied by 12). Two, per-patient-per-year (PPPY) costs for each drug-drug and drug-disease interaction were defined as the total costs to the plan associated with that drug-drug and drug-disease interaction divided by the total number of patients who had that particular drug-drug and drug-disease interaction during the study year.

Factors used as covariates in the regression of the likelihood of hemorrhage included member age (as of January 1, 2004), gender, average dose of warfarin in the study year, the medical specialty of the first prescriber for the first warfarin claim, the number of different prescribing physicians for the patient for any medication, a diagnosis for HF during that same time period (ICD-9-CM codes of 428.0, 428.22, 428.23, 428.32, 428.33, 428.42, 428.43), and days of 2004 warfarin therapy. Physicians were identified using the Drug Enforcement Administration (DEA) numbers listed on the pharmacy claims. Because the same physician sometimes has 2 DEA numbers for 2 different medical practice locations, the number of prescribers tends to have an upward bias. The number of warfarin-prescribing DEA numbers in a year was categorized into 3 groups of 1, 2-3, or 4 or more. Physician specialty of the first provider of warfarin was categorized into 3 groups: cardiovascular, primary practitioner (family practitioner, general practitioner, internal medicine), and other physician specialties (Table 3).

To evaluate the dose of warfarin, we used the formula: dose = (strength x quantity)/days supply entered by the pharmacist. We averaged the doses of every individual for the study period and divided the members into 3 groups: (1) less than or equal to 5 mg/day, (2) between 5 mg/day and 7.5 mg/day, and (3) greater than 7.5 mg/day. The length of warfarin therapy was defined as the sum of the days supply of warfarin during the study year for every patient. For the last prescription during the year, if the fill date plus days supply was greater than the remaining days in the year, then the days supply was equal to the end date of the year minus the last prescription date. We categorized length of warfarin therapy into 3 groups: (1) less than or equal to 120 days, (2) between 121 days and 180 days, and (3) greater than 180 days. This variable is interpreted primarily as a proxy for exposure to warfarin therapy. Also, this variable may act as a proxy for eligibility. For this reason, we do not attempt to draw substantive conclusions based on this variable.

The data manipulation and statistical analyses were conducted in the SAS 8.2 system. Univariate statistics were used to describe the distribution of the study variables and the frequencies of the drug-drug and drug-disease interaction. Bivariate relationships were evaluated with either chi-square or t tests as appropriate. Logistic regression was used to evaluate the relative risk of hemorrhage in users of warfarin monotherapy and of warfarin users with drug-drug and drug-disease interactions. The comparison group in the logistic regression comprised the members who received warfarin therapy but no other drug therapy. Therefore, the odds ratios (ORs) produced were estimates of the relative risk of hemorrhage when taking warfarin concomitant with selected drugs and diseases.

### Table 3: Description of Study Sample of Warfarin Users (n=17,895)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Sample (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and gender</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9,067 (50.6)</td>
</tr>
<tr>
<td>Age in years, mean [SD]</td>
<td>64.29 [14.6]</td>
</tr>
<tr>
<td>Warfarin dose and length of therapy</td>
<td></td>
</tr>
<tr>
<td>Warfarin dose in mg†, mean [SD]</td>
<td>6.18 [4.6]</td>
</tr>
<tr>
<td>Less than 120 days of warfarin therapy, n (%)</td>
<td>7,209 (40.3)</td>
</tr>
<tr>
<td>121-180 days of warfarin therapy, n (%)</td>
<td>2,518 (14.1)</td>
</tr>
<tr>
<td>181+ days of warfarin therapy, n (%)</td>
<td>8,168 (45.7)</td>
</tr>
<tr>
<td>Prescriber numbers and medical specialty</td>
<td></td>
</tr>
<tr>
<td>Unique prescriber numbers, mean [SD]</td>
<td>4.22 [2.6]</td>
</tr>
<tr>
<td>Primary practitioner, n (%)</td>
<td>9,305 (52.0)</td>
</tr>
<tr>
<td>Cardiovascular specialty, n (%)</td>
<td>3,564 (19.9)</td>
</tr>
<tr>
<td>Other specialty, n (%)</td>
<td>2,245 (12.6)</td>
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<tr>
<td>Missing specialty, n (%)</td>
<td>2,781 (15.5)</td>
</tr>
<tr>
<td>Medical diagnoses for hemorrhage or heart failure</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage‡, n (%)</td>
<td>2,634 (14.7)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>1,875 (10.5)</td>
</tr>
<tr>
<td>Liver disease, n (%)</td>
<td>315 (1.8)</td>
</tr>
<tr>
<td>Most frequent hemorrhage diagnosis codes, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic disorder due to circulating anticoagulants (ICD-9-CM=286.5)</td>
<td>640 (2.6)</td>
</tr>
<tr>
<td>Hemorrhage of gastrointestinal tract, unspecified (ICD-9-CM=578.9)</td>
<td>295 (1.7)</td>
</tr>
<tr>
<td>Hemorrhage of rectum and anus (ICD-9-CM=569.3)</td>
<td>223 (1.3)</td>
</tr>
<tr>
<td>Hemorrhage from nose, nosebleed (ICD-9-CM=784.7)</td>
<td>151 (0.8)</td>
</tr>
<tr>
<td>Hemoptysis (cough with hemorrhage; pulmonary hemorrhage NOS, (ICD-9-CM=786.3)</td>
<td>93 (0.5)</td>
</tr>
</tbody>
</table>

* Fill date for pharmacy claims from October 1, 2003, to September 30, 2004. ‡ The distribution of warfarin pharmacy claims by strength: 12,710 (11.9%) 1 mg, 11,537 (10.8%) 2 mg, 8,649 (8.1%) 2.5 mg, 6,671 (6.3%) 3 mg, 8,993 (8.4%) 4 mg, 47,290 (44.3%) 5 mg, 3,276 (3.1%) 6 mg, 4,037 (3.8%) 7.5 mg, 3,514 (3.2%) 10.0 mg. † Hemorrhage or heart failure was defined by more than 100 ICD-9-CM codes (see Table 2).
Results

Of the 1.7 million members eligible for drug and medical benefits during the study period (see below), 17,895 members filled at least 1 pharmacy claim for warfarin and were selected for study (Table 3). Warfarin users averaged age 64.3 years with a standard deviation of 14.6 years. The study patients received prescriptions from an average of 4.2 unique DEA numbers, although most warfarin users (73%) received all of their prescriptions from 5 or fewer prescribers.

Of the 17,895 members who used warfarin during the study year, 2,634 (14.7%) were diagnosed with hemorrhage subsequent to filling a prescription for warfarin. The most common hemorrhage diagnoses by ICD-9-CM code were hemorrhagic disorder due to circulating anticoagulants (286.5), hemorrhage of gastrointestinal tract, unspecified, (578.9) hemorrhage of rectum and anus (569.3), hemorrhage from nose, nosebleed (784.7), hemoptysis (cough with hemorrhage, and pulmonary hemorrhage not otherwise specified, (786.3) (Table 3). Of the warfarin users, 1,260 (7.0%) concomitantly received prescriptions for amiodarone, 4,906 (27.4%) for an NSAID/COX-2, 3,385 (18.9%) for cephalosporin, 779 (4.4%) for metronidazole, and 761 (4.3%) for fibric acid derivative. Of the NSAID/COX-2 drug-drug or drug-disease interactions, 3,114 (63.5%) were associated with a COX-2 inhibitor, 1,340 (26.6%) with a nonselective NSAID, and 452 (9.2%) with both. Of warfarin users, 315 (1.8%) had a diagnosis of liver disease and 1,875 (10.5%) had a diagnosis of HF. Table 4 reports the average age and gender for each drug-drug or drug-disease interaction pair.

The prevalence of hemorrhage, defined as a binary variable, was regressed on indicators for each of these drug-drug or drug-disease interactions as well as member age, gender, average warfarin dose, number of days of warfarin therapy, number of unique prescribers, a diagnosis of HF, and physician specialty of the first prescriber of warfarin during the study year. The result of logistic regression is presented in Table 5. Liver disease in warfarin users was associated with a significant increase in the likelihood of hemorrhage when compared with warfarin monotherapy users ($P<0.05$). Patients who were taking warfarin and who had a diagnosis of HF were 1.559 times as likely to be diagnosed subsequently with hemorrhage. Warfarin used concomitant with cephalosporins or metronidazole also was associated with significantly increased likelihood of hemorrhage over warfarin use alone ($P<0.05$). Members who received prescriptions from multiple prescribers were at higher risk of hemorrhage ($P<0.05$). Compared with patients who had their first prescription for warfarin written by a cardiologist, patients who received their first prescription for warfarin from any other specialist were associated with a higher risk of hemorrhage ($P<0.05$). Women were somewhat more likely to hemorrhage than men ($P<0.05$), and younger members were somewhat more likely to be diagnosed with hemorrhage ($P<0.05$). The risk of hemorrhage increased with the duration of warfarin use in days. The average daily dose of warfarin and concomitant use of amiodarone and fibric acid derivatives were not significantly related to the hemorrhage rate. NSAID/COX-2 use was negatively related to the likelihood of hemorrhage, although marginally so.

Overall, a cost of $0.40 PMPM was associated with hemorrhage events recorded in medical or hospital claims within 7 days of receipt of a warfarin fill. When disaggregated by the associated drug-drug or drug-disease interaction, the PMPM cost varied considerably according to the volume of the patients with each interaction. The PMPM cost associated with hemor-
Discussion
Over the last several years, there has been increasing focus on avoidable medical errors, especially avoidable medication errors. Although warfarin is a drug that has been on the market for many years and has significant use in the medical community, it remains a drug that can put a patient at risk for an adverse drug event.

Of the warfarin drug and disease interactions in the study, concomitant use of 5 drug categories occurred with a sufficient statistical frequency to evaluate the risk of hemorrhage. In addition, we evaluated comorbid heart disease and liver disease. Of the 5 drug categories, cephalosporins and metronidazole increased the likelihood of hemorrhage. Both cephalosporins and metronidazole are antibiotics, suggesting short-term use. Cephalosporins and metronidazole both have a relatively high incidence of use with warfarin and are associated with an increase in the likelihood of hemorrhage. This would suggest that greater care must be taken by clinicians who dispense these medications. Increased member-physician communication and education as well as programs such as pharmacy messaging, academic detailing of physicians by pharmacists, and electronic messaging as well as programs such as pharmacy messaging, may help prevent this type of drug-drug or drug-disease interaction. Although the PMPM for warfarin-liver disease drug-drug or drug-disease interactions is relatively low ($0.02), the PPPY is relatively high ($1,135). The PPPY values for the other drug-drug or drug-disease interactions found to be statistically significant were $896 for warfarin-metronidazole, $663 for warfarin in HF, and $569 for warfarin-cephalosporins. For individuals who used only warfarin, the average PPPY was $293, the lowest of any of the PPPY values.

### TABLE 5 Risk of Hemorrhage Among Warfarin Users*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio†</th>
<th>0.05 Wald Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>1.149†</td>
<td>1.053</td>
</tr>
<tr>
<td>Decrease in age of 1 year</td>
<td>1.009†</td>
<td>1.006</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.559†</td>
<td>1.373</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.764†</td>
<td>1.360</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1.157†</td>
<td>1.043</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>1.578†</td>
<td>1.321</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0.980</td>
<td>0.827</td>
</tr>
<tr>
<td>Fibrac acid derivatives</td>
<td>0.823</td>
<td>0.660</td>
</tr>
<tr>
<td>NSAIDs/COX-2s</td>
<td>0.904†</td>
<td>0.820</td>
</tr>
<tr>
<td>Average dose of warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 mg</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>5 mg to 7.5 mg</td>
<td>1.077</td>
<td>0.966</td>
</tr>
<tr>
<td>More than 7.5 mg</td>
<td>1.071</td>
<td>0.962</td>
</tr>
<tr>
<td>Days of warfarin therapy</td>
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<td></td>
</tr>
<tr>
<td>≤120 days</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>120 to 180 days</td>
<td>1.571†</td>
<td>1.373</td>
</tr>
<tr>
<td>More than 180 days</td>
<td>1.953†</td>
<td>1.771</td>
</tr>
<tr>
<td>Number of unique prescriber numbers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>1.284†</td>
<td>1.082</td>
</tr>
<tr>
<td>≥4</td>
<td>1.799†</td>
<td>1.519</td>
</tr>
<tr>
<td>Prescriber specialty†</td>
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<tr>
<td>Cardiovascular</td>
<td>1.000</td>
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</tr>
<tr>
<td>Primary care practitioner</td>
<td>1.216†</td>
<td>1.097</td>
</tr>
<tr>
<td>Other specialty</td>
<td>1.303†</td>
<td>1.117</td>
</tr>
<tr>
<td>Likelihood ratio= 441.29, 17 df, P ≤0.001.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Regression analysis.
† Odds ratios are significant at P ≤0.05.
‡ The medical specialty of the first prescriber of warfarin therapy.
COX-2 = cyclooxygenase-2; NSAIDs = nonsteroidal anti-inflammatory drugs.

Hemorrhage was highest for the group of warfarin-NSAID/COX-2 drug-drug or drug-disease interactions ($0.16), warfarin users with no drug-drug or drug-disease interactions ($0.13), and warfarin-cephalosporins drug-drug or drug-disease interactions ($0.09). The PMPM costs for the other drug-drug or drug-disease interactions in this analysis ranged from $0.02 for liver disease to $0.05 for fibrac acid derivatives (Table 6).

The costs are ranked differently when the denominator used is the number of patients who have been identified with each drug-drug or drug-disease interaction. Although the PMPM for warfarin-liver disease drug-drug or drug-disease interactions is relatively low ($0.02), the PPPY is relatively high ($1,135). The PPPY values for the other drug-drug or drug-disease interactions found to be statistically significant were $896 for warfarin-metronidazole, $663 for warfarin in HF, and $569 for warfarin-cephalosporins. For individuals who used only warfarin, the average PPPY was $293, the lowest of any of the PPPY values.
term use itself may be related to hemorrhage, or it may take longer for symptoms of some of the adverse events to become acute enough to warrant a visit to a physician. This finding suggests physicians' review of chronic warfarin use may help prevent adverse reactions. Warfarin use requires long-term monitoring. Members may not comply with testing, which may increase the frequency of hemorrhage.

Tools such as prospective drug utilization reviews (pDURs) were recently evaluated by Malone et al. with a nonrandom sample of 46 million Americans. In this study, they found that the pDUR employed by the PBM in the current study rejected between 19% and 46% of claims that may result in a drug-drug interaction, depending on the class of drugs. On one hand, these rates testify to the success of the pDUR program. On the other, many drugs with the potential for drug-drug interactions are prescribed despite the warnings. In their discussion of why these drug-drug interactions continue to occur, Malone et al. identified 1 factor as lack of physician awareness of drug-drug interactions. They cited a survey of physicians in the Southern California Veterans Affairs Healthcare System as properly identifying only 44% of drug-drug interactions as well as further evidence that physicians and pharmacists did not recognize many drug-drug interactions.

Compounding the problem of physician awareness may be the number of different practitioners who prescribe drugs for patients and the dispersion of medical and pharmacy records. We found that the likelihood of hemorrhage is greater for patients receiving prescriptions from a greater number of prescriber numbers. This suggests that programs to increase communication between practitioners also may help reduce adverse reactions to drug-drug interactions. The results obtained in this study, in which 2 out of 5 possible drug-drug interactions were associated with a statistically significant increased risk of hemorrhage compared with warfarin use alone, suggest that further research is needed to identify which of the many possible drug-drug interactions require focus for communication interventions with prescribers. Programs that give providers information on the complete prescription history of their patients, similar to the point-of-service (POS) drug utilization review (DUR) services that PBMs provide to pharmacies, may help to reduce drug-drug interactions. Other tools such as electronic prescribing and direct consultations with physicians should be used to reinforce contraindications and risks of drug-drug or drug-disease interactions when prescribing warfarin. Disease management programs focusing on HF should be engaged in monitoring appropriate warfarin prescribing.

The risk associated with the use of warfarin necessitates greater attention by physicians when initiating therapy and on an ongoing basis. Even with this increased focus by physicians, the risk of drug-drug or drug-disease interactions still exists because of the fragmentation found in health care delivery today. Due to the lack of transparency of care across all caregivers, organizations such as PBMs and managed care organizations will also have a role in this process. These organizations, by virtue of their aggregation of all claims associated with a patient, need to work with physicians to get them all the information necessary to make a clinically informed prescribing decision. This can be done through safety checks for all community or mail-service pharmacy prescriptions with feedback to the prescribing physician and through support of electronic prescribing.

The costs associated with drug-drug or drug-disease interactions seem to warrant attention. When calculated per member and per drug-drug or drug-disease interaction, costs associated with drug-drug or drug-disease interactions suggest that, in addition to reducing the risk of hemorrhage and further complications, a program to reduce drug-drug or drug-disease interactions could result in significant plan savings as well. Many drug-drug or drug-disease interactions are approved by physicians or pharmacists despite POS DUR alerts that notify pharmacists of potential drug-drug or drug-disease interactions at the time of claim adjudication.

**Limitations**

One of the primary limitations of this study is that data on the international normalized ratio (INR) are not available. These data on the INR would allow researchers to better evaluate whether the anticoagulant therapy for these patients was within therapeutic range. Another limitation is that the combination of the large number of potential warfarin-drug interactions com-

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**TABLE 6** Direct Medical Costs of Hemorrhage Events in One Year

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
<th>Total * Cost ($)</th>
<th>PMPM ($)†</th>
<th>PPTY ($)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin-NSAIDs/COX-2s</td>
<td>4,906</td>
<td>3,348,186</td>
<td>0.16</td>
<td>682</td>
</tr>
<tr>
<td>Warfarin only</td>
<td>9,147</td>
<td>2,679,841</td>
<td>0.13</td>
<td>293</td>
</tr>
<tr>
<td>Warfarin-cephalosporins</td>
<td>3,385</td>
<td>1,927,007</td>
<td>0.09</td>
<td>569</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1,875</td>
<td>1,242,693</td>
<td>0.06</td>
<td>663</td>
</tr>
<tr>
<td>Warfarin-fibrin acid derivs</td>
<td>761</td>
<td>1,041,948</td>
<td>0.05</td>
<td>1,369</td>
</tr>
<tr>
<td>Warfarin-metronidazole</td>
<td>779</td>
<td>697,671</td>
<td>0.03</td>
<td>896</td>
</tr>
<tr>
<td>Warfarin-amiodarone</td>
<td>1,260</td>
<td>560,132</td>
<td>0.03</td>
<td>445</td>
</tr>
<tr>
<td>Warfarin-liver disease</td>
<td>315</td>
<td>357,368</td>
<td>0.02</td>
<td>1,135</td>
</tr>
<tr>
<td>Total</td>
<td>17,895</td>
<td>8,191,464</td>
<td>0.40</td>
<td>458</td>
</tr>
</tbody>
</table>

Note: Claims with dates of service from October 1, 2003, through September 30, 2004.

* Plan cost for all medical and hospital claims with a hemorrhage diagnosis (see Table 2 for a list of the codes) within 7 days of a pharmacy claim for warfarin. Some patients are represented in more than 1 row in the table, causing the sum of the rows to exceed the reported total cost.

† PMPM is cost per member per month for approximately 1.7 million members.

‡ PPTY is cost per patient per year for the specific drug-drug or drug-disease interaction in this row of the table.

COX-2 = cyclooxygenase-2, NSAIDs = nonsteroidal anti-inflammatory drugs.
bined with the limited size of the dataset made it impossible to evaluate the impact of all potential warfarin drug interactions. Yet another limitation is that we did not control for disease severity in this study.

Perhaps foremost in this study, the relationship between warfarin use and hemorrhage events is merely a temporal one, and it is not possible to attribute directly the hemorrhage claims to the use of warfarin alone or in combination with disease or drugs known to interact with warfarin. It is also possible that the costs attributed to hemorrhage events are overstated since claims aggregation was based on having a hemorrhage diagnosis on any field on the medical or hospital claim, not necessarily being the primary diagnosis on the claim.

We could not control for the use of over-the-counter products, herbal products (e.g., garlic, ginkgo biloba), or food consumed by the study subjects that is known to interact with warfarin. The lack of data on over-the-counter drugs may have had an impact on the results for the relative risk of hemorrhage in patients who received both warfarin and prescription NSAID/COX-2 therapy. Several natural products contain substances that have coumarin, salicylate, or antiplatelet properties. A theoretical risk for potentiation of the pharmacologic activity of warfarin exists, therefore, when these herbs or food are taken with warfarin. In addition, we did not distinguish hemorrhage by organ.

Another limitation is that the identification of drugs dispensed to inpatients is not available from administrative claims. Another consideration in the interpretation of these results is that only those bleeding events that resulted in visits to physicians or hospitals and were diagnosed as hemorrhages were considered in this analysis. Therefore, the nonsignificant results for some of the drug-drug or drug-disease interactions may mask problems that were not detected by physicians, not diagnosed, or not recorded as such. Further, the small incidence of some of the drug-drug or drug-disease interactions limited our ability to distinguish outcomes for many of the drug-drug or drug-disease interactions.

**Conclusions**

The analysis of administrative claims data confirms the observations from clinical trials and further quantifies the incidence of warfarin drug-drug or drug-disease interactions associated with hemorrhage events. The frequency of concomitant warfarin use with metronidazole was 4.4% and with oral cephalosporins, 18.9%; 22.7% and 17.2%, respectively, of this concomitant use was associated with at least 1 hemorrhage event. There was no higher risk of a hemorrhage event for the concomitant use of warfarin with NSAIDs, including COX-2 inhibitors, amiodarone, or fibrin acid derivatives, compared with the use of warfarin alone, with absolute rates of hemorrhage in the range of 13.1% to 14.8% for these 3 drug-drug combinations versus a 14.2% prevalence of hemorrhage for use of warfarin alone. Patients diagnosed with liver disease or HF are more likely to experience a hemorrhage event while on warfarin therapy.

**DISCLOSURES**

No outside funding supported this research. Author Kui Zhang served as principal author of the study. Study concept and design were contributed by Zhang. Data collection was the work of Zhang and author Christopher Young; data interpretation was primarily the work of Zhang and Young, with input from author Jan Berger. Writing of the manuscript was primarily the work of Young, with input from Zhang, its revision was primarily the work of Young, with major input from Berger and input from Zhang. The authors disclose no potential bias or conflict of interest relating to this article.

**REFERENCES**


Physician Conformity and Patient Adherence to ACE Inhibitors and ARBs in Patients With Diabetes, With and Without Renal Disease and Hypertension, in a Medicaid Managed Care Organization

CATHERINE E. COOKE, PharmD, BCPS, and HUGH FATODU, RPh

ABSTRACT

BACKGROUND: The American Diabetes Association (ADA) recommends using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients with diabetes and comorbid hypertension or renal disease.

OBJECTIVE: To examine the use of ACE inhibitors and ARBs in members of a Medicaid managed care organization (MCO) with diabetes and a diagnosis of hypertension and/or kidney disease to determine to what extent (1) physicians are conforming to the recommended course of treatment according to ADA guidelines published in 2002 and still current and (2) patients are adhering to their prescribed therapy.

METHODS: Patients with diabetes were identified using medical claims from a Medicaid MCO in Maryland of approximately 118,000 members continuously enrolled during the study period. To be included in the cohort, members had to have at least 1 medical claim containing a diagnosis of diabetes mellitus from April 1, 2001, through March 31, 2002, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 250.xx. Additional medical claims during the same time period for hypertension, ICD-9-CM code 401.xx, and renal disease, ICD-9-CM codes for nephropathy (582.81 or 582.9), proteinuria (791.0), or diabetic nephropathy (250.40 or 250.42 for type 2 diabetes only), were used to categorize the cohort into 4 subgroups: diabetes and renal disease with hypertension, diabetes and renal disease without hypertension, diabetes and without renal disease and without hypertension. Pharmacy claims for ACE inhibitors and ARBs were obtained from July 1, 2001, through June 30, 2002, and utilization was defined as the patient having at least 1 pharmacy claim for an ACE inhibitor or an ARB. Patient adherence with ACE inhibitor or ARB therapy was measured using medication possession ratio (MPR) and median gap between prescription refills.

RESULTS: There were 1,698 patients, approximately 2.3% of the total continuously enrolled members, with 1 or more medical claims containing an ICD-9-CM code of 250.xx for diabetes mellitus. The average age was 48 ± 13.2 years for the total sample, and nearly 70% of the patients were women (1,188 women and 510 men). Only 13% of the patients in the sample had medical claim evidence of any renal involvement, while 63% of the study patients had hypertension. A total of 915 patients (53.9%) had at least 1 pharmacy claim for an ACE inhibitor or an ARB, accounting for 7,934 unique pharmacy claims, an average of 8.7 pharmacy claims per patient. Patients with renal involvement and without hypertension (47%) were less likely to receive an ACE inhibitor or an ARB than patients with renal involvement and hypertension (85%) (P < 0.001). Patients without renal involvement or hypertension (19%) were less likely to receive an ACE inhibitor or an ARB than patients with hypertension and no renal involvement (71%) (P < 0.001). The MPR for all patients was 0.77 (± 0.26). MPR and median gap between prescription refills.

CONCLUSIONS: Physicians’ conformity is high when they prescribe an ACE inhibitor or ARB for patients with diabetes and hypertension but is lower than expected for patients with diabetes and renal disease but without hypertension. Older patients in this analysis of persons aged 18 to 65 years adhered more to their ACE inhibitor or ARB therapy.

KEYWORDS: Diabetes mellitus, Hypertension, Angiotensin-converting enzyme (ACE) inhibitor, Angiotensin receptor blocker (ARB), Adherence

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Note: An editorial on the subject of this article appears on pages 690-91 of this issue.

A pproximately 18 million people in the United States, or about 6% of the country’s population, have diabetes mellitus, 5 million of whom remain undiagnosed.1 According to the Centers for Disease Control and Prevention (CDC), about 73% of adults with diabetes have high blood pressure of >130/80 mmHg or use prescription medication for hypertension.1 The American Diabetes Association (ADA) concurs that hypertension is an extremely common comorbid condition in diabetes and that patients with both type 1 and type 2 diabetes mellitus are at risk for hypertension.2 Patients with comorbid hypertension and diabetes have an increased likelihood of macrovascular complications, such as coronary artery disease and stroke, as well as microvascular complications, such as retinopathy and nephropathy.2,3

Management of Diabetic Hypertension

According to the CDC, controlling hypertension in patients with diabetes can reduce macrovascular complications by approximately 33% to 50% and microvascular complications by approximately 33%.1 The United Kingdom Prospective Diabetes Study (UKPDS) Group concluded that each 10 mmHg decrease in mean systolic blood pressure is associated with a 12% reduction in risk for any complication related to diabetes, 15% for death related to diabetes, 11% for myocardial infarction, and 37% for microvascular complications.4 The UKPDS found that ACE inhibitors had similar outcomes and were better tolerated when compared with beta-blockers.5 Although this distinction is important for patients using antihypertensive monotherapy, the majority of patients with diabetes will require at least 2 antihypertensives.6 Angiotensin-converting enzyme (ACE) inhibitors also have a favorable effect on cardiovascular outcomes as demonstrated in the Heart Outcomes Prevention Evaluation (HOPE) study.7,8 Researchers in the HOPE study found that the ACE inhibitor
Thus, according to the ADA, ACE inhibitors and angiotensin receptor blockers (ARBs) decrease the progression of albuminuria and nephropathy, they may not be tolerated. In a study of patients with diabetes and hypertension, the reported prevalence of cough associated with use of ACE inhibitors was 14.9%, with ramipril significantly reduced the risk of a composite outcome of sudden death and resuscitated cardiac arrest by 21% compared with placebo (P = 0.028) in patients without systolic dysfunction.7

Many clinical studies have shown that ACE inhibitors decrease the risk of adverse outcomes, including macrovascular and microvascular complications, in patients with diabetes and hypertension.2-4,7,9,10 Thus, according to the ADA, ACE inhibitors are first-line therapy for most patients with diabetes and hypertension.2-4,7 ACE inhibitors and angiotensin receptor blockers (ARBs) decrease the progression of albuminuria and nephropathy and therefore are considered first-line therapy for the prevention and progression of nephropathy.2,4,7 Both the 2002 and 2004 ADA guidelines state, “In the treatment of albuminuria/nephropathy, both ACE inhibitors and ARBs can be used.”2-4,7 Some clinicians are concerned with the potential adverse effects on renal function of patients with renal disease using an ACE inhibitor or an ARB. However, HOPE trial researchers concluded that ACE inhibitors reduce the risk of cardiovascular disease in patients with mild renal insufficiency (defined as baseline serum creatinine <2.3 mg/dl) and should not be withheld because of a moderate increase in serum creatinine.9

Although ACE inhibitors are considered first-line for the management of diabetes in patients with comorbid hypertension and nephropathy, they may not be tolerated. In a study of patients with diabetes and hypertension, the reported prevalence of cough associated with use of ACE inhibitors was 14.9%, with 4.7% of patients interrupting treatment as a result.11 Similarly, the UKPDS Group noted that 4% of patients receiving captopril discontinued therapy due to cough.7 ARBs are considered appropriate agents if patients cannot tolerate an ACE inhibitor.9,10

**Study Objectives**

This study examined the utilization of ACE inhibitors and ARBs in members of a Medicaid managed care organization (MCO) with diabetes with and without a diagnosis of hypertension and/or kidney disease to determine whether physicians are conforming to the recommended course of treatment in published guidelines and whether patients are adhering to their prescribed therapy.

**Methods**

**Study Design and Participants**

Pharmacy and medical claims databases from a Medicaid MCO in Maryland were obtained and used to identify the study cohort. The Medicaid MCO was founded in 1997 as a partnership between a large university-based health system and federally qualified health centers, and serves as one of the MCOs for HealthChoice, Maryland’s statewide mandatory managed care program. The Medicaid MCO had approximately 118,000 members during the study period from March 1, 2001, through June 30, 2002. As part of the pharmacy benefit through the Medicaid MCO, members had no copayment for prescriptions. The pharmacy benefit had no mail-service option, and prescription quantities were limited to a 30-day supply.

The study sample included members aged 18 to 65 years who were continuously enrolled during the study period, with medical and pharmacy coverage. Continuous medical and pharmacy coverage was defined as no gap in coverage of more than 30 days.

Patients were included in the study cohort if they had at least 1 medical claim for diabetes mellitus using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 250.xx from April 1, 2001, to March 31, 2002. Additional medical claims during this time period for renal disease, ICD-9-CM code for nephropathy (582.81 or 582.9), proteinuria (791.0), or diabetic nephropathy (250.40 or 250.42 for type 2 diabetes only), and essential hypertension (401.xx), including malignant hypertension (401.0), benign hypertension (401.1), and hypertension not otherwise specified (401.9), were obtained to categorize the cohort into the 4 distinct groups.

* P <0.001 compared with use in renal involvement without hypertension (chi-square test).
† P <0.001 compared with use without renal involvement or hypertension (chi-square test).
ACE=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker.

**Figure 1** Utilization of ACE Inhibitor and ARB

Patients were included in the study cohort if they had at least 1 medical claim for diabetes mellitus using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 250.xx from April 1, 2001, to March 31, 2002. Additional medical claims during this time period for renal disease, ICD-9-CM code for nephropathy (582.81 or 582.9), proteinuria (791.0), or diabetic nephropathy (250.40 or 250.42 for type 2 diabetes only), and essential hypertension (401.xx), including malignant hypertension (401.0), malignant hypertension (401.0), benign hypertension (401.1), and hypertension not otherwise specified (401.9), were obtained to categorize the cohort into the 4 distinct groups.

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† P <0.001 compared with use without renal involvement or hypertension (chi-square test).
ACE=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker.

## Methods

### Study Design and Participants

### Study Objectives
renal disease and without hypertension (Figure 1).

The dataset for pharmacy claims with dates of service from July 1, 2001, through June 30, 2002, contained the following fields: unique deidentified patient number, patient age (as of July 1, 2001), patient sex, prescription number, date filled, drug name, strength, new or refill status, MCO paid quantity, and number of paid days supplied. All data conformed to Health Insurance Portability and Accountability Act patient privacy standards, and the dataset was delivered to the researchers with deidentified patient information. The University of Maryland Institutional Review Board assigned exempt status to the research protocol.

**Pharmacy Claims Analysis**

Using the pharmacy claims for ACE inhibitors and ARBs for the cohort for dates of service from July 1, 2001, through June 30, 2002, patients were categorized by their first dispensed prescription into either ACE inhibitor, ARB, or combination product. Utilization was defined as the member having at least 1 pharmacy claim for an ACE inhibitor or an ARB therapy during the study period. Patient adherence with ACE inhibitor or ARB therapy was measured using medication possession ratio (MPR) and median gap between prescription refills.

For all adherence evaluations, ACE inhibitors or ARBs were considered together. If a patient was switched from an ACE inhibitor to an ARB or vice versa, days supply for both the ACE inhibitor and ARB were summed. Days supply for the first therapy was truncated to the number of days from the last dispensed fill of the medication to the start of the new drug product. For patients who had an ACE inhibitor or ARB added to their existing ARB or ACE inhibitor therapy, respectively, patient adherence measures were considered only for the initial drug.

In this study, MPR was calculated by adding the total days supply for all ACE inhibitor or ARB pharmacy claims and dividing by the total possible days supply of ACE inhibitor or ARB from the date when the prescription was originally dispensed. The denominator of total possible days supply consisted of the number of days from the first fill until the end of the study period to account for prescriptions filled later in the study period. We chose to truncate the MPR at 1.0 to prevent overestimation of MPR (e.g., last fill greater than days supply remaining in the evaluation period). Patients were categorized, based on their MPR, into 3 categories: “Good” (MPR ≥0.8), “Poor” (MPR 0.5-<0.8) and “Very Poor” (MPR <0.5).

The median gap of time in days between prescription refills is another measure of patient adherence. The median gap in this study was calculated as the median of the number of days a prescription was refilled in relation to the end of the days supply of the previous prescription. A positive median gap represents the number of days the member was late in filling subsequent refills, with larger numbers denoting lower adherence.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient Characteristics and Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Cohort of Members With Diabetes</td>
</tr>
<tr>
<td>Male, number (%)</td>
<td>n=1,698</td>
</tr>
<tr>
<td>Mean age [SD]</td>
<td>48 [13.2]</td>
</tr>
<tr>
<td>Number (%) receiving antihyperglycemic agents</td>
<td>1,307 (77)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,072 (63)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>215 (13)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB (at least 1 claim)</td>
<td>915 (53.9)</td>
</tr>
<tr>
<td>Mean [SD] # of ACE inhibitor or ARB claims per patient</td>
<td>8.7 [5.0]</td>
</tr>
<tr>
<td>Mean [SD] days supply per ACE inhibitor or ARB claim</td>
<td>29.4 [2.4]</td>
</tr>
<tr>
<td>Mean [SD] days supply per patient</td>
<td>279 [108]</td>
</tr>
<tr>
<td>Mean MPR (SD)*</td>
<td>0.77 [0.26]</td>
</tr>
<tr>
<td>Mean [SD] of median gap in days between prescription fills</td>
<td>7.9 [25.6]</td>
</tr>
</tbody>
</table>

*Positive correlation between MPR and age (Pearson r test) P <0.001.

**Results**

**Member Demographics**

The study sample included a total of 1,698 members with diabetes mellitus, approximately 2.3% of total continuously enrolled members. The average age was 48 ± 13.2 years for the total sample, and nearly 70% of the patients were women (n=1,188 women and n = 510 men). Seventy-seven percent of these patients were taking antihyperglycemic agents, including insulin and oral hypoglycemic agents. As defined by ICD-9-CM codes, only 13% of the sample had any renal involvement while 63% of the study sample had hypertension (Figure 1).

**ACE Inhibitor or ARB Utilization**

Of the 1,698 patients with diabetes mellitus, 915 (53.9%) had at least 1 pharmacy claim for an ACE inhibitor or an ARB, accounting for 7,934 unique pharmacy claims during the study period (Table 1). Patients with a pharmacy claim for an ACE inhibitor or ARB each had an average of 8.7 pharmacy claims (± 5.0 SD) with an average days supply per pharmacy claim of 29.4 (± 2.4) days. Patients had an average days supply of 279 (±108 SD) days, out of the 365-day study period (Table 1).
Physician Conformity and Patient Adherence to ACE Inhibitors and ARBs in Patients With Diabetes, With and Without Renal Disease and Hypertension, in a Medicaid Managed Care Organization

Nearly 8 of 10 (76.8%) patients who received an ACE inhibitor or ARB prescription had their first fill in the first quarter of the study period (July 1, 2001, through September 30, 2001). Of the 915 patients with pharmacy claims, 631 (69.0%) were women and 284 were men (31.0%), with a mean age of 50.2 (± 9.4 years). This reflects the health plan’s managed Medicaid population, as there is a 2:1 ratio of women to men in members aged 40 years and older. There were 62 patients younger than 18 to 65 years and MPR (± 0.26) (Student t test). However, we found a significant positive correlation (r² = 0.021) between age in the range of 18 to 65 years and MPR (P < 0.001).

Utilization of ACE inhibitors or ARBs in patients with disease indications for drug therapy of hypertension and/or renal disease was calculated to be 72.6%. Only 18.5% of patients with diabetes without either of these indications were receiving an ACE inhibitor or an ARB. There were no significant differences in utilization based on age or sex. ACE inhibitors or ARBs were used in 73.5% of diabetes patients with hypertension and 78.6% of diabetes patients with renal disease. Presence of hypertension was a significant predictor for members both with and without renal disease to receive an ACE inhibitor or an ARB (P < 0.001). Patients with renal involvement and without hypertension (47%) were less likely to receive an ACE inhibitor or an ARB than members with hypertension and no renal involvement (85%) (P < 0.001). Patients without renal involvement or hypertension (19%) were less likely to receive an ACE inhibitor or an ARB than members with hypertension and no renal involvement (71%) (P < 0.001). In patients without hypertension, renal disease was a significant predictor of ACE inhibitor or ARB use (P < 0.001).

**Medication Possession Ratio**

The average MPR for all patients was 0.77 (± 0.26) (median = 0.88), with a range of 0.08 to 1.0 (Table 3). A majority of patients (60.4%) had “good” adherence to therapy, with an MPR ≥0.8. However, 21.9% of members had “poor” adherence, with MPR ranging from 0.5 to <0.8, and 17.7% had “very poor” adherence, with an MPR of less than 0.5. MPR did not differ significantly by sex, with male members having an MPR of 0.78 (± 0.26) and female members having an MPR of 0.77 (± 0.26) (Student t test). However, we found a significant positive correlation (r² = 0.021) between age in the range of 18 to 65 years and MPR (P < 0.001).

**Table 2:** Initial ACE Inhibitor or ARB Prescription by Drug and Category

<table>
<thead>
<tr>
<th>Drug Category and Name (by Generic Only)</th>
<th>Number of Patients</th>
<th>%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor*</td>
<td>707</td>
<td>77.3</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>453</td>
<td>49.5</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>95</td>
<td>10.4</td>
</tr>
<tr>
<td>Quinapril</td>
<td>79</td>
<td>8.6</td>
</tr>
<tr>
<td>Captopril</td>
<td>31</td>
<td>3.4</td>
</tr>
<tr>
<td>Enalapril maleate</td>
<td>31</td>
<td>3.4</td>
</tr>
<tr>
<td>Ramipril</td>
<td>17</td>
<td>1.9</td>
</tr>
<tr>
<td>Benazepril</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>ACE inhibitor/diuretic combination†</td>
<td>68</td>
<td>7.4</td>
</tr>
<tr>
<td>Lisinopril/hydrochlorothiazide</td>
<td>55</td>
<td>6.0</td>
</tr>
<tr>
<td>Quinapril/hydrochlorothiazide</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>Captopril/hydrochlorothiazide</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Fosinopril/hydrochlorothiazide</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Enalapril/hydrochlorothiazide</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>ARB*</td>
<td>107</td>
<td>11.7</td>
</tr>
<tr>
<td>Losartan</td>
<td>45</td>
<td>4.9</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>44</td>
<td>4.8</td>
</tr>
<tr>
<td>Valsartan</td>
<td>17</td>
<td>1.9</td>
</tr>
<tr>
<td>Candesartan</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>ARB/diuretic combination†</td>
<td>27</td>
<td>3.0</td>
</tr>
<tr>
<td>Losartan/hydrochlorothiazide</td>
<td>12</td>
<td>1.3</td>
</tr>
<tr>
<td>Irbesartan/hydrochlorothiazide</td>
<td>10</td>
<td>1.1</td>
</tr>
<tr>
<td>Valsartan/hydrochlorothiazide</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>ACE inhibitor/calcium channel blocker combination†</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>Amlodipine/benazepril</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Trandolapril/verapamil ER</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Percentages do not add to 100% due to rounding.
† Depicts combination drugs. Note: Patients in the ACE inhibitor or ARB categories may also receive additional prescriptions for other antihypertensive agents such as a diuretic, beta-blocker, or calcium channel blocker, which are not categorized here. Instead, patients are categorized by product and not by entire medication regimen.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ER = extended release.
Median Gap between Prescription Refills

The median gap in days between prescription refills for a given patient is another method of measuring adherence with prescribed therapy. The overall mean of the median gap for patients was 7.9 (± 25.6 SD) days (Table 3). No significant difference in mean gap by sex was detected, with male members having a mean gap of 8.6 (± 27.0) days and female members having a mean gap of 7.6 (± 25.0 SD) days (Student t test). In addition, there was no significant difference in the median gap by age (Pearson r).

Discussion

Approximately 54% of all members with diabetes were prescribed an ACE inhibitor or an ARB in this sample cohort from a Medicaid MCO population. Most of the patients who received ACE inhibitors or ARBs in our sample were women (69.0%) between 45 and 64 years of age (73.8%).

The proportion of ACE inhibitor use was 85.4%, while ARB use was 14.6%. Examining those members with concomitant hypertension and diabetes, we found a 73.5% prescription rate for ACE inhibitors or ARBs, which is higher than in previously reported studies during the same time period. A similar patient population of Tennessee MCO members had only a 46.2% prescription rate for ACE inhibitors in patients with type 2 diabetes and hypertension in the year 2000.12 In a study in Bahrain the same year, approximately 40% of patients with diabetes and hypertension (as determined from pharmacy claims without medical claims) seen by family physicians were receiving ACE inhibitors.13 A more recent study using data from 2003 found a similar utilization rate to our study—the authors analyzed pharmacy claims from members of a commercial MCO with diabetes and hypertension and found a 71.6% utilization rate for ACE inhibitors or ARBs.14

We used several measures to proxy physician conformity to existing physician practice guidelines in place during the study period and patient adherence with the prescribed ACE inhibitor or ARB therapy. In our sample, 85% of members with renal involvement and hypertension and 71% of members with hypertension (without renal involvement) were prescribed ACE inhibitor or ARB medications. According to the ADA practice guideline in place at the time of the study, which is still current today, it is recommended that patients with a diastolic blood pressure of >80 mmHg and a systolic blood pressure of >130 mmHg be treated (Figure 2).15 We used the ICD-9-CM codes for hypertension to identify patients with diabetes and hypertension who should receive treatment. Overall, 73.5% of members (788 of 1072, Figure 1) with diabetes and hypertension in our sample were prescribed ACE inhibitor or ARB medications.

Similarly, for patients with diabetes and renal disease, there was an overall utilization rate of ACE inhibitors or ARBs of 78.6% (169 of 215, Figure 1). The 2002 and 2004 (most recent) ADA guidelines specifically address diabetic nephropathy and recommend the use of ACE inhibitors or ARBs for patients with diabetes and albuminuria/nerphopathy.8,10 These rates show high physician conformity with the evidence found in the medical literature for patients with diabetes and comorbid renal disease or hypertension.15

Overall, 72.6% of members (806 of 1,110) with disease indications appropriate for ACE inhibitor/ARB therapy had at least 1 pharmacy claim for these agents. The largest discrepancy appeared in patients with diabetes with renal disease but without hypertension, in whom there was 47.4% use of an ACE inhibitor or an ARB (18 of 38). However, these 20 patients with renal disease but without hypertension and not receiving either an ACE inhibitor or an ARB represented only 1.2% of the sample cohort in this study.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor/ARB utilization (at least 1 claim)</td>
<td>284</td>
<td>631</td>
<td>915</td>
</tr>
<tr>
<td>Mean MPR [SD]</td>
<td>0.78 [0.26]</td>
<td>0.77 [0.26]</td>
<td>0.77 [0.26]</td>
</tr>
<tr>
<td>Good MPR: MPR ≥ 0.8 (“good”) (%)</td>
<td>172 (60.6)†</td>
<td>381 (60.4)</td>
<td>553 (60.4)</td>
</tr>
<tr>
<td>Poor MPR: 0.5 ≤ MPR &lt;0.8 (%)</td>
<td>59 (20.8)†</td>
<td>141 (22.3)</td>
<td>200 (21.9)</td>
</tr>
<tr>
<td>Very poor MPR: MPR &lt;0.5 (%)</td>
<td>53 (18.7)†</td>
<td>109 (17.3)</td>
<td>162 (17.7)</td>
</tr>
<tr>
<td>Mean [SD] median gap (days)</td>
<td>8.6 [27.0]</td>
<td>7.6 [25.0]</td>
<td>7.9 [25.6]</td>
</tr>
</tbody>
</table>

*All nonsignificant differences in adherence parameters by sex (Student t test and x² statistic).†The totals of these 3 categories is greater than 100% due to rounding.
Conclusion

Physicians' conformity was high when they prescribed an ACE inhibitor or an ARB for patients with diabetes and hypertension, which was expected on the basis of the medical evidence available in 2001-2002 during the study period. However, physicians' conformity was lower than expected among patients with diabetes and renal disease but without hypertension, who could still benefit from the use of ACE inhibitors or ARBs to prevent microvascular complications. However, the untreated target population in this cohort of MCO patients was less than 2%—20 patients with renal disease but without hypertension and not receiving either an ACE inhibitor or an ARB.

Overall, patient adherence with therapy was generally good as measured by MPR. Adherence to ACE inhibitor or ARB therapy was directly associated with age. A potential concern in these study results was an average delay of approximately 8 days in refilling prescriptions for ACE inhibitors or ARBs in this cohort, for which cost was not a barrier to adherence with therapy since members received their prescriptions at no charge ($0 copayment). Medicaid MCOs may choose to target those patients our study identified as being the most at risk for failing to receive and adhere to ACE inhibitor or ARB therapy—

MPR can be an indirect measure of physician conformity with existing practice guidelines as well as a direct measure of patient adherence with therapy. A majority (60.4%) of members had MPR rates that can be classified as “good” (≥0.8). Our 60.4% rate of adherence was lower than the rate from Wannemacher et al.16 (77%), but that could be because of the difference in how MPR was calculated and our decision to truncate the MPR at 1.0 for individual patients as well as the difference in drugs studied. Our study was limited to ACE inhibitors and ARBs only (combined with other agents), while Wannemacher et al. also evaluated other antihypertensives, including beta-blockers, calcium channel blockers, diuretics, and a miscellaneous class (used as single agents).

In our sample, older patients (within the age range of 18 to 65 years in the study) tended to adhere more to ACE inhibitor or ARB therapy, as evidenced by higher MPRs. Patient adherence with therapy was also measured by median gap and, on average, patents were more than a week late refilling their next ACE inhibitor or ARB prescription.

Grant et al.17 reported high patient compliance for taking all diabetes-related medicine at 6.7 (± 1.1) out of the previous 7 days. In addition, patients in their sample reported the highest 7-day adherence for agents related to the treatment of hypertension and hyperlipidemia (6.8 of 7 days for both).17 Grant et al. were further able to tie patient adherence to perception of the medications' ability to improve their symptoms and protect their future health. They concluded that “patients' perceptions of the immediate and future benefit of prescribed medications have a significant impact on their adherence.”16

While self-reported adherence and persistence may be overestimated, Grant et al. were able to show the important role that patient comprehension of the value of treatment plays in compliance with therapy.

Limitations

The results of this study should be interpreted with some caution because of certain limitations in the dataset and in the methodology. First and foremost, we measured adherence but required as little as 1 pharmacy claim as an inclusion criterion for the study. Second, this study used data from 2001 and 2002 and, although recommendations for ACE inhibitor and ARB use have not changed, the use may be different in future years. Third, we might have missed some patients with renal disease based on the ICD-9-CM code of 585, chronic renal failure, which was not part of the inclusion criteria.

Lastly, our methods relied heavily on ICD-9-CM coding, first, in identifying patients with diabetes mellitus to define the study population and second, in defining patients with renal involvement and hypertension. This point has several implications: (1) we did not require patients to have multiple medical claims for any of the medical diagnoses (i.e., diabetes, hypertension, renal disease) or concomitant antihyperglycemic claims for any of the medical diagnoses (i.e., diabetes, hypertension, renal disease) or concomitant antihyperglycemic agents, so false-positive classification was possible; (2) we did not classify patients based on diagnoses at the beginning of the study period, creating the possibility that the classification of some patients did not reflect their condition during the entire study period, and (3) as with all medical claims, we had no way to evaluate the accuracy of the coding, which might have been incomplete. There are many reasons medical claims coding might be inaccurate or incomplete, including accidental or intentional miscoding.

Physician prescribing of ACE inhibitors or ARBs was determined from administrative claims. Administrative claims data do not reveal what drugs might have been prescribed but not dispensed or if the dispensed drug was actually used by the patient. Patients who had discontinued therapy before the study period because of intolerance or for other reasons would have underestimated appropriate ACE inhibitor/ARB prescribing. In addition, the adherence parameters could have been affected by the use of drug samples obtained from physician offices, which would result in underestimates of adherence. In our population, we believe sample use to be low because physicians tend to reserve samples for patients without pharmacy benefits or poor insurance coverage. This Medicaid population had broad coverage of ACE inhibitors and ARBs and no copayment.

The pharmacy claims in our study were limited to ACE inhibitors and ARBs prescribed either as a single agent or in combination with another agent, such as a diuretic or a calcium channel blocker. For this reason, previous published studies evaluating all antihypertensive medication might not be comparable.
younger patients and patients diagnosed with diabetes and renal disease but without hypertension.

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DISCLOSURES

No outside funding supported this research. Author Catherine E. Cooke served as principal author of the study. Study concept and design were contributed by Cooke and author Hugh Fatodu. Data collection was the work of Fatodu; data interpretation was primarily the work of Cooke, with input from Fatodu. Writing of the manuscript was primarily the work of Cooke, with input from Fatodu; its revision was the work of both authors. Cooke discloses no potential bias or conflict of interest relating to this article. Fatodu discloses that he has received honoraria from Novartis, the maker of branded ARBs.

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Liver and Thyroid Monitoring in Ambulatory Patients Prescribed Amiodarone in 10 HMOs

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ABSTRACT

BACKGROUND: Amiodarone can cause liver and thyroid toxicity, but little is known about compliance with laboratory tests to evaluate liver and thyroid function among ambulatory patients who are dispensed amiodarone.

OBJECTIVES: The primary objective of this study was to identify the proportion of ambulatory patients who had liver aminotransferase and thyroid function tests during amiodarone therapy. Secondary objectives were to (1) describe factors associated with receipt of laboratory tests and (2) determine the accuracy of administrative data for assessing aminotransferase and thyroid function monitoring.

METHODS: This retrospective cohort study was conducted at 10 health maintenance organizations (HMOs) for the dates of service from January 1, 1999, through June 30, 2001. Participants included 1,055 patients dispensed amiodarone for at least 180 days within this date range; these patients were not necessarily new starts on amiodarone. Administrative claims data were analyzed to assess the percentage of patients with completed alanine/aspartate aminotransferase and thyroid function tests. Depending on the HMO site, electronic or paper medical records were reviewed to evaluate the validity of administrative claims data. Logistic regression models were used to explore factors associated with receipt of laboratory tests.

RESULTS: Both aminotransferase and thyroid function tests were completed in 53.3% of patients within a 210-day follow-up period that included the 180-day period of amiodarone dispensings plus 30 days. Thyroid function, with or without liver function (aminotransferase tests), was assessed in 61.9% of patients, and aminotransferase tests, with or without thyroid function, were assessed in 68.2% of patients. After adjusting for patient characteristics and site, the factor most strongly associated with having both types of laboratory tests evaluated was concomitant therapy with a statin (adjusted odds ratio [OR] 1.55; 95% confidence interval [CI], 1.05-2.29). Other factors associated with having both types of laboratory tests evaluated included the number of outpatient visits in the 6 months before the period of amiodarone dispensings (adjusted OR 1.06; 95% CI, 1.00-1.13 for each additional 5 visits) and living in a neighborhood where a higher median percentage of people had a high school or higher education (adjusted OR 1.09; 95% CI, 1.00-1.18 for every 10% increase in educational level at the block level). There was no association between monitoring and patient illness severity as measured by the number of comorbid conditions. On the basis of an evaluation of a randomly selected subset of 104 patient records, the sensitivity and specificity of automated data were 94.2% and 85.7% for aminotransferase tests and 83.3% and 81.1% for thyroid function tests, respectively.

CONCLUSIONS: Approximately half of ambulatory patients dispensed amiodarone received both recommended laboratory tests for liver and thyroid function. Improved rates of testing for liver aminotransferase and thyroid function are needed for patients who receive amiodarone.

KEYWORDS: Amiodarone, Laboratory monitoring, Thyroid, Aminotransferase, Liver, Patient safety

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in some situations, liver enzyme abnormalities resolve spontaneously despite continuing therapy. As is true of routine laboratory monitoring of many drugs, at this time for amiodarone, it is only assumed that routine monitoring of the aminotransferase liver enzymes (alanine and/or aspartate [ALT/AST] aminotransferases) and thyroid function improves patient outcomes. Despite the lack of direct evidence linking laboratory-value monitoring to outcomes, an agreed-upon and widely recommended strategy to prevent or minimize the adverse effects of amiodarone on liver and thyroid function is to monitor aminotransferase and thyroid function in patients taking maintenance doses of the drug. The manufacturers recommend in product labeling “regular” or “periodic” monitoring of these laboratory tests for all patients prescribed amiodarone. Others (see Table 1) recommend obtaining both ALT/AST and thyroid function tests (total and/or free thyroxine [T4] and/or thyroid-stimulating hormone [TSH] at specific frequencies; for example, every 3 or 6 months during therapy.

The extent to which monitoring aminotransferases and thyroid function is conducted as a patient safety measure among patients prescribed amiodarone is not well known. The few studies that evaluated liver and thyroid monitoring among patients prescribed amiodarone were conducted at single clinics and/or included fewer than 100 patients. These small studies all determined that thyroid function and liver enzymes were monitored in low percentages (23%-42%) of patients. The current study was therefore undertaken to determine the rates of monitoring thyroid function and liver aminotransferases among ambulatory patients dispensed amiodarone therapy across 10 sites. Secondary objectives included determining the accuracy of administrative claims data for aminotransferase and thyroid function monitoring and describing patient factors associated with monitoring. The information provided here can be used as a basis for quality improvement initiatives by individual clinicians as a reminder to monitor individual patients and by organizations to link electronic data to help ensure recommended safety monitoring in patients receiving maintenance amiodarone therapy.

**Methods**

This retrospective study included members of 10 health maintenance organizations (HMOs) receiving chronic amiodarone therapy, defined as continuing amiodarone dispensings for at least 180 days. Participating HMO sites included members of the HMO Research Network (HMORN) Center for Education and Research in Therapeutics (CERTs). The HMORN CERTs has been described elsewhere. In brief, the HMORN CERTs organizations include staff, groups, networks, independent practice associations, and mixed-model HMOs that serve racially and ethnically diverse populations and provided health care for approximately 7 million people in more than 1,000 locations in the year 2000. The Institutional Review Board of each participating HMO approved this study.

The study sample was drawn from a dataset of 2,020,037 individuals, consisting of approximately 200,000 randomly selected health plan members from practices in each of the

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**Table 1 Examples of Aminotransferase and Thyroid Function Monitoring Recommendations for Amiodarone**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Aminotransferase(s)</th>
<th>Recommended Monitoring Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson and Podrid (1991)</td>
<td>Aminotransferase(s)</td>
<td>Baseline, then every 3-6 months</td>
</tr>
<tr>
<td>Singh (1997)</td>
<td>Aminotransferase(s)</td>
<td>Baseline, then every 3-6 months</td>
</tr>
<tr>
<td>Hilleman et al. (1998)</td>
<td>Aminotransferase(s)</td>
<td>Baseline, then every 3-6 months</td>
</tr>
<tr>
<td>Sanoski et al. (1998)</td>
<td>Aminotransferase(s)</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>Product labeling (1999)</td>
<td>Aminotransferase(s)</td>
<td>On a regular basis in patients on relatively high maintenance doses</td>
</tr>
<tr>
<td>Goldschlager et al. (2000)</td>
<td>Aminotransferase(s)</td>
<td>Baseline, then every 6 months</td>
</tr>
<tr>
<td>Pollak and Shafer (2004)</td>
<td>Aminotransferase(s)</td>
<td>“…Baseline, 1, 3, and 6 months, and then semianually…”</td>
</tr>
<tr>
<td>Amiodarone (drug evaluation) (2005)</td>
<td>Aminotransferase(s)</td>
<td>“…Prior to initiating therapy…every 6 months thereafter.”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Thyroid Function</th>
<th>Recommended Monitoring Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson and Podrid (1991)</td>
<td>Thyroid Function</td>
<td>Baseline, then every 3-6 months</td>
</tr>
<tr>
<td>Singh (1997)</td>
<td>Thyroid Function</td>
<td>Baseline, then every 3-6 months</td>
</tr>
<tr>
<td>Hilleman et al. (1998)</td>
<td>Thyroid Function</td>
<td>Baseline, then every 3-6 months</td>
</tr>
<tr>
<td>Sanoski et al. (1998)</td>
<td>Thyroid Function</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>Product labeling (1999)</td>
<td>Thyroid Function</td>
<td>Prior to initiation and periodically thereafter</td>
</tr>
<tr>
<td>Goldschlager et al. (2000)</td>
<td>Thyroid Function</td>
<td>Baseline, then every 6 months</td>
</tr>
<tr>
<td>Amiodarone (drug evaluation) (2005)</td>
<td>Thyroid Function</td>
<td>Baseline, after 2-3 months of therapy and then periodically (once every few months)</td>
</tr>
</tbody>
</table>
Liver and Thyroid Monitoring in Ambulatory Patients Prescribed Amiodarone in 10 HMOs

The sampling scheme and demographic distribution of this population have been previously described. The date range of this dataset was claims with dates of service from January 1, 1999, through June 30, 2001. We identified patients who had continuous health plan membership with pharmacy benefits during the study period, disregarding gaps of fewer than 60 days. To be included in this study, patients must have received a dispensing of amiodarone in the 18-month period from July 1, 1999, through December 31, 2000, plus continuing dispensings for the subsequent 180 days (Table 2). Dispensings for the subsequent 180 days were determined for each patient by the number of amiodarone dispensings to that patient multiplied by the days supply for each dispensing to that patient. Thus, each patient’s follow-up period was determined by the patient’s individual 180-day period of amiodarone usage. To meet the definition of continuing dispensings, no interval between prescription refills could be greater than the dispensed days supply plus 1.5 times the dispensed days supply. A dispensing gap was ignored if it was less than 1.5 times the dispensed days supply. For example, a patient dispensed a 30-day supply met the criterion of continuing dispensing if no more than 75 days (30 days + [1.5] 30 days) elapsed between the date of one dispensing and the date of the subsequent dispensing. At least 8 of the 10 participating HMOs offered mail-order pharmacy services during part or all of the study period. However, during the study time frame, only 1 or 2 offered a separate mail-order benefit (with a greater days supply).

Because each HMO had its own administrative database platform, the format and content of the claims datasets varied by site. The study dataset was extracted using a standardized work plan distributed to, and run by, research programmers at each site. At some of the sites, claims for laboratory tests performed or the results were reported. Codes for laboratory tests were evaluated according to standard coding methods such as the Current Procedural Terminology codes or organization-specific codes and included codes for both single tests and for test panels that included one or more of the aminotransferase or thyroid function tests, including general health panel laboratory tests that include ALT, AST, and TSH (Table 3).

To assess the accuracy of the administrative claims data, we examined a random sample of medical records of study patients from the 10 sites. For purposes of this study, the medical record was considered the “gold standard,” meaning that the medical record served as the basis of comparison and was assumed to be more accurate. The laboratory monitoring information contained within the medical records (i.e., the presence of laboratory test results and the dates the laboratory tests were performed) was considered the gold standard. Abstractors were instructed to review all information in the medical record for the time frame of interest (e.g., laboratory printouts, progress notes, information from outside consults, etc.) to ensure abstraction of ALT/AST or thyroid function testing.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the administrative claims data were determined in comparison with the data abstracted from the medical records. Sensitivity was defined as the proportion of patients who had an aminotransferase or thyroid function test performed that was documented in the medical record and who also had an administrative claims code for the

### Table 2: Sample Selection

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Number of Patients Dropped</th>
<th>Number (%) of Patients Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients dispensed amiodarone*</td>
<td>–</td>
<td>2,770 (100)</td>
</tr>
<tr>
<td>Patients with at least 6 months membership prior to the first amiodarone dispensing in the study period†</td>
<td>285</td>
<td>2,483 (89.7)</td>
</tr>
<tr>
<td>Patients with at least 2 pharmacy claims for amiodarone therapy‡</td>
<td>1,041</td>
<td>1,444 (52.1)</td>
</tr>
<tr>
<td>Patients with at least 180 days of continuing amiodarone therapy†</td>
<td>389</td>
<td>1,055 (38.1)</td>
</tr>
</tbody>
</table>

* Patients who received a dispensing of amiodarone between July 1, 1999, and December 31, 2000.
† Membership date range included January 1, 1999, through June 30, 2001, disregarding gaps of less than 60 days.
‡ The interval between prescription refills could not be greater than the dispensed days supply plus 1.5 times the dispensed days supply.
Liver and Thyroid Monitoring in Ambulatory Patients Prescribed Amiodarone in 10 HMOs

Associations between patient characteristics and laboratory monitoring were assessed using logistic regression modeling. Characteristics considered in univariate regression models included site, age group (in 5-year increments), sex, CDsum, outpatient visits, hospitalization in the 6 months prior to the laboratory monitoring/ongoing amiodarone therapy period, the 3 SES variables, and the presence or absence of concomitant therapy with a statin. We developed a generalized estimating equations (GEE) logistic regression model with HMO site as a cluster variable. The GEE model initially included those variables with P < 0.10 in the univariate regression models: age group, outpatient visits, poverty, education, and concomitant therapy with a statin. CDsum was not included in the GEE model because it correlated with outpatient visits (Spearman correlation coefficient = 0.39). Customary residual and influential statistics were examined to assess model fit and evaluate outliers. Analyses were conducted using SAS Version 9.1 (SAS Institute Inc., Cary, NC). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.
Liver and Thyroid Monitoring in Ambulatory Patients Prescribed Amiodarone in 10 HMOs

Results

We identified 1,055 patients who met the study eligibility criteria for chronic amiodarone therapy (Tables 2 and 4). Both thyroid function and liver aminotransferases were monitored in 53.3% of patients (95% confidence interval [CI], 50.2%-56.3%). The 10 participating HMO sites had significant variability in monitoring, with a range across sites from 23.1% to 78.4% of patients monitored (Figure 1). Liver aminotransferases were monitored in 68.2% of patients (95% CI, 65.3%-71.1%), and thyroid function tests were monitored in 61.9% of patients (95% CI, 58.9%-64.8%). Among all patients with thyroid tests evaluated, thyroid function monitoring comprised 97.2% TSH tests and 2.8% T4 tests. Patients with and without monitoring did not differ in age, sex, estimated number of chronic diseases, hospitalization, or poverty level (Table 4). When patient characteristics and site were controlled, only 3 factors were associated with monitoring: concomitant therapy with a statin (crude odds ratio (OR), 1.55; 95% CI, 1.21-1.98; adjusted OR, 1.55; 95% CI, 1.05-2.30), number of outpatient visits in the 6 months before the period of ongoing amiodarone dispensings (crude OR, 1.07; 95% CI, 1.01-1.14; adjusted OR, 1.06; 95% CI, 1.00-1.13 for each additional 5 visits), and living in a neighborhood where a higher median percentage of people had a high school or higher education (crude OR, 1.15; 95% CI, 1.02-1.28; adjusted OR, 1.09; 95% CI, 1.00-
1.18 for every 10% increase in educational level at the block level) (scaled deviance = 1.370). There were no overly influential or outlying observations. The effect of clustering by site was small (exchangeable working correlation = 0.056).

Medical records of 104 study patients prescribed chronic amiodarone therapy were abstracted. The sensitivity, specificity, PPV, and NPV of the administrative claims in comparison with the abstracted medical records for ALT/AST and thyroid function monitoring were good to excellent as shown in Table 5.

■ Discussion

We found that only about one half (53.3%) of patients receiving ongoing therapy with amiodarone had laboratory tests conducted to assess liver injury and thyroid function during an approximately 7-month period. The laboratory test findings from administrative claims data in our study were validated with medical record review. We demonstrated that administrative claims records at these sites were sufficiently sensitive and specific to be useful in determining whether laboratory testing was conducted.

Our finding that many patients prescribed amiodarone do not have recommended laboratory monitoring is important. However, the percentage of patients with laboratory monitoring in our study is actually higher than the 23% to 42% of patients documented as monitored in the small number of other published abstracts and studies.7,17,19

Stelfox et al. found that increases in comorbidity were associated with a lower likelihood of monitoring.7 We found no association between monitoring and the surrogate measure we used to determine the number of comorbid conditions, that is, CDsum, but these differing findings may not be directly comparable because Stelfox used a different measure of comorbidity than that used in our study (Charlson Comorbidity Index in the Stelfox et al. study and CDsum in the present study).7 Similar to Stelfox et al., we found no association between monitoring and patients' age or sex.7

In our study, the factor most strongly associated with a higher rate of monitoring was concomitant therapy with a statin, a drug for which ALT/AST monitoring is also recommended; patients treated with a statin had a 55% greater likelihood of receiving monitoring of both liver enzymes and thyroid function. We found
Liver and Thyroid Monitoring in Ambulatory Patients Prescribed Amiodarone in 10 HMOs

### TABLE 5
Accuracy of Administrative Claims Data in Comparison to the Medical Record* for Assessing Prevalence of Liver Aminotransferase and Thyroid Function Test Monitoring

<table>
<thead>
<tr>
<th>Measure of Validity** (n=104 Medical Records)</th>
<th>% (Range Across Sites)</th>
<th>Alinate/Aspartate Aminotransferase</th>
<th>Thyroid Function Tests†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>94.2 (77.8-100)</td>
<td>83.3 (42.9-100)</td>
<td></td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>85.7 (50.0-100)</td>
<td>81.1 (50.0-100)</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>92.9 (71.4-100)</td>
<td>88.7 (66.7-100)</td>
<td></td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>88.2 (33.3-100)</td>
<td>73.2 (33.3-100)</td>
<td></td>
</tr>
</tbody>
</table>

* The research design defined the medical record as the benchmark for determination of monitoring of amiodarone side effects via laboratory tests. For example, sensitivity was defined as the proportion of patients who had an aminotransferase (or thyroid function) test conducted that was documented in the medical record, who also had an administrative claims code for the test. Specificity was the proportion of patients who did not have an aminotransferase (or thyroid function) test documented in the medical record who also did not have a claims code for the test. The positive predictive value was the proportion of patients who had the laboratory test conducted, according to administrative data, who were true positives according to the medical record. The negative predictive value was the proportion of patients who did not have the laboratory test conducted, according to administrative data, who were true negatives according to the medical record.

† Thyroid function tests = thyroid-stimulating hormone (TSH), thyroxine (T4), or triiodothyronine (T3).

The majority of patients remain euthyroid 10,19 patients receiving amiodarone are recommended to have routine ALT/AST monitoring. Persistent elevations in liver enzymes alert clinicians to weigh the risks and benefits of amiodarone dosage reduction or discontinuation often weighing the risk of sudden cardiac death against the risk of liver toxicity. An elevation of ALT/AST of 2 to 3 times the upper limit of normal, or a doubling of the ALT/AST in a patient with an elevated baseline value, is cited as the level above which amiodarone dosage reduction can be appropriate 10,19 Withdrawal of the drug does not guarantee prompt reversal of organ toxicity, however, because tissue concentrations of amiodarone persist for weeks to months following drug withdrawal; during long-term oral administration, the mean half-life following cessation of therapy is 40 to 49 days.9,30

Both hyper- and hypothyroidism are associated with amiodarone therapy and can develop in normal thyroid glands as well as in glands with preexisting abnormalities.10 The amiodarone molecule contains large amounts of inorganic iodine (a 600 mg per day amiodarone dosage provides 225 mg of iodide) and amiodarone-induced thyrotoxicosis occurs due to either iodine-induced excessive thyroid hormone synthesis or to a thyroid destructive process caused by the drug or iodine.10 Amiodarone inhibits peripheral conversion of T4 to T3 with resulting increases in both serum T4 and reverse T3 accompanied by a reduction in serum T3.10 The majority of patients remain euthyroid despite these biochemical changes, and it is important to specifically evaluate serum TSH levels to determine whether thyroid dysfunction is present. We found that the vast majority (97.2%) of the thyroid function tests obtained in patients in our study were TSH tests.

Hyperthyroidism occurs in about 2% of amiodarone-treated patients, with a higher incidence in patients with prior inadequate dietary iodine.9 Hyperthyroidism can be especially hazardous in the patient population prescribed amiodarone because of the possibility of arrhythmia breakthrough or aggravation.11,12 Hyperthyroidism associated with amiodarone therapy has occurred anywhere from 1 to 73 months after initiation of therapy and with amiodarone dosages ranging from 200 to 600 mg per day; thus, ongoing monitoring is important.

Limitations

A potential limitation to our study was that we primarily used health plan administrative claims data to determine whether laboratory tests were completed, and some would argue that the medical record is the more accurate source of this information. However, the sensitivity and specificity of the claims data were shown to be good to excellent for documenting completion of

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* The research design defined the medical record as the benchmark for determination of monitoring of amiodarone side effects via laboratory tests. For example, sensitivity was defined as the proportion of patients who had an aminotransferase (or thyroid function) test conducted that was documented in the medical record, who also had an administrative claims code for the test. Specificity was the proportion of patients who did not have an aminotransferase (or thyroid function) test documented in the medical record who also did not have a claims code for the test. The positive predictive value was the proportion of patients who had the laboratory test conducted, according to administrative data, who were true positives according to the medical record. The negative predictive value was the proportion of patients who did not have the laboratory test conducted, according to administrative data, who were true negatives according to the medical record.

† Thyroid function tests = thyroid-stimulating hormone (TSH), thyroxine (T4), or triiodothyronine (T3).

The incidence of amiodarone-associated adverse events is dependent on both dose and duration of therapy, with risk believed primarily to exist with daily dosages exceeding 400 mg and durations of therapy exceeding 10 to 12 months.4,9,26 Most adverse effects are mild, but toxicity of sufficient severity to require discontinuing amiodarone has been reported in up to one fourth of patients.9,10 Liver injury with amiodarone includes, very rarely, acute hepatitis (only 13 cases reported through 2002) and liver failure (<5 reported cases),9,10,27-29 but the liver injury seen most often is symptomatic (<3% of patients) or asymptomatic (up to 24% of patients), sometimes transient, abnormal elevation of ALT and/or AST.

Inadequate dietary iodine.

Liver injury with amiodarone includes, very rarely, acute hepatitis (only 13 cases reported through 2002) and liver failure (<5 reported cases),9,10,27-29 but the liver injury seen most often is symptomatic (<3% of patients) or asymptomatic (up to 24% of patients), sometimes transient, abnormal elevation of ALT and/or AST. Because both clinical liver disease and fatalities have occurred with amiodarone use,9,10,28 patients receiving amiodarone are recommended to have routine ALT/AST monitoring. Persistent elevations in liver enzymes alert clinicians to weigh the risks and benefits of amiodarone dosage reduction or discontinuation often weighing the risk of sudden cardiac death against the risk of liver toxicity. An elevation of ALT/AST of 2 to 3 times the upper limit of normal, or a doubling of the ALT/AST in a patient with an elevated baseline value, is cited as the level above which amiodarone dosage reduction can be appropriate.10,19 Withdrawal of the drug does not guarantee prompt reversal of organ toxicity, however, because tissue concentrations of amiodarone persist for weeks to months following drug withdrawal; during long-term oral administration, the mean half-life following cessation of therapy is 40 to 49 days.9,30

Both hyper- and hypothyroidism are associated with amiodarone therapy and can develop in normal thyroid glands as well as in glands with preexisting abnormalities.10 The amiodarone molecule contains large amounts of inorganic iodine (a 600 mg per day amiodarone dosage provides 225 mg of iodide) and amiodarone-induced thyrotoxicosis occurs due to either iodine-induced excessive thyroid hormone synthesis or to a thyroid destructive process caused by the drug or iodine.10 Amiodarone inhibits peripheral conversion of T4 to T3 with resulting increases in both serum T4 and reverse T3 accompanied by a reduction in serum T3. The majority of patients remain euthyroid despite these biochemical changes, and it is important to specifically evaluate serum TSH levels to determine whether thyroid dysfunction is present. We found that the vast majority (97.2%) of the thyroid function tests obtained in patients in our study were TSH tests.

Hyperthyroidism occurs in about 2% of amiodarone-treated patients, with a higher incidence in patients with prior inadequate dietary iodine.9 Hyperthyroidism can be especially hazardous in the patient population prescribed amiodarone because of the possibility of arrhythmia breakthrough or aggravation.11,12 Hyperthyroidism associated with amiodarone therapy has occurred anywhere from 1 to 73 months after initiation of therapy and with amiodarone dosages ranging from 200 to 600 mg per day; thus, ongoing monitoring is important.

Limitations

A potential limitation to our study was that we primarily used health plan administrative claims data to determine whether laboratory tests were completed, and some would argue that the medical record is the more accurate source of this information. However, the sensitivity and specificity of the claims data were shown to be good to excellent for documenting completion of
these tests. Also, it is possible that not all medication dispensing or laboratory testing was captured by the HMO data systems. For example, 21.8% of the patients in this study were hospitalized during the study period. The patients who were dispensed amiodarone therapy and who were hospitalized during the study follow-up period may have received laboratory tests for aminotransferase and/or thyroid function during the hospitalization that were not captured in the data available to us because laboratory tests completed during hospitalizations were contained in the dataset for only some of the participating sites. Therefore, our measured rates of laboratory monitoring may underreport actual rates of monitoring. However, if the laboratory testing information was not available in the dataset, as evidenced by the good negative predictive value (Table 5), the laboratory testing information was also not available in the medical record and therefore not available to the prescriber to use in managing the ambulatory medical care of the patient.

Aside from the missing data for laboratory monitoring that may have occurred during a hospital stay in the follow-up period, the administrative claims data used in this study are sufficiently accurate to be useful to assess laboratory monitoring. As is true of all studies where prescriber intent is not directly determined, we could not separate laboratory tests conducted for the purpose of assessing the potential toxicity of amiodarone from laboratory tests conducted for other reasons that had nothing to do with amiodarone therapy. Further, we did not have information on amiodarone dosage and could not evaluate whether monitoring was associated with higher daily drug dosages or if dosages were adjusted based on laboratory results. Although we do not know the percentage of abnormal test results among patients in this study, we believe it would be similar to previously published percentages.\(^4\)\(^5\)\(^6\)\(^7\) In a randomized intervention trial conducted during 2003 at one of the sites that participated in the current study, 15% of patients who were prescribed amiodarone and who received thyroid and/or aminotransferase laboratory testing as a result of the study intervention had abnormal test results.\(^3\)

There is the possibility that some patients were misclassified as continuing on amiodarone therapy. On the basis of the study definition of continuing dispensings, patients with as few as 2 dispensings of amiodarone in the 180-day dispensing period were included (Table 4). For example, a study patient with only 2 dispensings could have had dispensings of amiodarone for a 90-day supply on day 1 and day 91, and discontinued therapy for some reason on day 92.

We found variation in monitoring by HMO site (Figure 1). These HMOs differ in potentially critical patient and system factors, including geographic location, race and ethnicity of members, availability of an electronic medical record, and types and extent of clinical pharmacy programs, patient safety programs, and receipt of care from multispecialty clinics. This project was not designed to explore why one participating HMO had better rates of monitoring of ALT/AST and thyroid function than did another. However, it may be useful to understand, for example, how the characteristics of the HMO where 23.1% of patients dispensed amiodarone had ALT/AST and thyroid monitoring differed from the HMO where 78.4% of patients received monitoring (Figure 1). Knowledge of organizational characteristics and programs would augment our ability to implement decision support systems or other systematic mechanisms to assist in ensuring recommended safety monitoring in patients receiving amiodarone. It is also important to recognize that these data were collected 5 to 6 years ago, and the rates of monitoring for adverse effects associated with amiodarone therapy may be different today, although monitoring recommendations do not differ from those published 5 to 6 years ago.

Conclusions

The percentage of ambulatory patients who are prescribed amiodarone and who receive monitoring of liver enzymes and thyroid function needs improvement. Automated, administrative claims data can be appropriate to evaluate the prevalence of aminotransferase and thyroid function monitoring, but this source of information has limitations that should be recognized.

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DISCLOSURES

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Writing of the manuscript was primarily the work of Raebel, with input from Feldstein, Simon, Andrade, Lafata, Nelson, Gunter, Tolsma, and Platt; its revision was primarily the work of Raebel, with input from the coauthors. Platt discloses that he is a consultant to the Agency for Healthcare Research & Quality, the sponsor of this research; he also has served as a consultant to and/or received research grants from numerous other organizations, including the Centers for Disease Control & Prevention, The U.S. Food and Drug Administration, the National Institutes of Health, GlaxoSmithKline, Parke Davis, Pfizer, sanofi-aventis, SmithKlineBeecham, Tap Pharmaceuticals, and Wyeth. The coauthors disclose no potential bias or conflict of interest relating to this article.
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Relationship of the Use and Costs of Physician Office Visits and Prescription Drugs to Travel Distance and Increases in Member Cost Share

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ABSTRACT

BACKGROUND: The prescription drug benefit is commonly designed and managed as a stand-alone health insurance product without consideration of how the design of other medical benefits may impact its use.

OBJECTIVE: To determine the effects of member cost (copayment/coinsurance) increases on the relationship between the use of physician office visits and the type/tier of prescription medication purchased in a commercially insured population.

METHODS: Our research model utilized managed care organization member cost-share levels that were changed as part of the annual benefit renewal process to estimate the price–quantity–expenditure relationship between cost sharing and use of physician office visits/prescription drugs by benefit tier. The price–quantity–expenditure relationship was measured across a benefit copayment price change to determine the effect of a price increase on utilization/expenditures. We included the distance from the member’s residence to the physician’s office as a proxy for the time cost of an office visit. The study sample included 44,828 members who were fully insured for the full 12 months of 2002, continued coverage for the full 12 months of 2003, and whose benefit renewal occurred on January 1, 2003. We hypothesize that a relationship exists between office visit use and its expenditures and prescription drug use and its expenditures based on out-of-pocket cost. Hypotheses were tested using a least squares dummy variable regression model across claims records for years 2002 and 2003, containing consecutive yearly records for the same members. The unit of analysis was the member. Demand was estimated by benefit category and copayment tier to provide the study variables, price elasticity of demand, cross-price elasticity of demand, and distance elasticity. Expenditure is net health plan cost after subtraction of member cost share (including copayments, coinsurance, and deductibles). The expenditure categories in this study were pharmacy, medical office visits, and total health care costs.

RESULTS: Members with greater travel distance to a primary care physician (PCP) or specialty care physician (SCP) office experienced higher PCP and SCP visit utilization (distance elasticity = 0.164 and 0.202, respectively; P < 0.01). Greater travel distance to a PCP was also associated with higher tier-1 prescription use (0.048, P < 0.01) as well as higher total plan-paid (0.032, P < 0.05) and PCP expenditures (0.141, P < 0.01). Greater travel distance to an SCP was associated with higher use of drugs in all 3 pharmacy copayment tiers (0.085, 0.075, and 0.073 for tier 1, tier 2, and tier 3, respectively; P < 0.01 for each tier). The price effects of an increase in tier-1 copayments were fewer PCP office visits (-0.118, P < 0.01) but more SCP office visits (0.177, P < 0.01); SCP visits were also higher with increased tier-3 copayments (0.118, P < 0.01). Tier-2 prescription drug use decreased with higher office visit copayments (0.105, P < 0.05). Increased tier-1 copayments were associated with lower expenditures for PCP office visits (-0.146, P < 0.05) but higher expenditures for SCP office visits (0.149, P < 0.05). While increases in tier-2 copayments were associated with lower PCP (and -0.322, P < 0.01) and SCP (-0.453, P < 0.01) expenditures, increases in tier-3 copayments were associated with higher PCP (0.495, P < 0.01) and SCP (0.197, P < 0.05) expenditures.

CONCLUSIONS: A relationship exists between physician office visits and prescription drug use based on member cost share and time factors. Increases in office visit copayments were associated with decreased use of drugs in the tier-2 pharmacy benefit category. Increases in tier-2 pharmacy benefit copayment levels were associated with lower PCP/SCP expenditures, but increases in tier-3 pharmacy benefit copayment levels were associated with higher PCP/SCP expenditures. The distance to a physician’s office was directly proportional to the number of office visits. Separation of the management of pharmacy and medical benefits may have significant cost implications for consumers, employers, and health plans. Therefore, optimal management of medical and pharmacy benefits may require a coordinated strategy and tactics.

KEYWORDS: Physician office visit, Copayment, Coinsurance, Benefit tier, Own-price elasticity, Cross-price elasticity, Expenditure

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implementation of optimal strategies for managing total medical costs, including the pharmacy benefit. It is our contention that a relationship exists between the utilization of pharmacy benefits and medical benefits. As such, segregating pharmacy claims from medical claims and making them inaccessible to medical claims analysts limits the ability of insurers to optimize their health care management strategy.

Characterizations of consumer preferences for visiting certain physicians’ offices or purchasing certain prescription drugs have traditionally been analyzed by looking at the specific benefits without considering the potential for substitution or complementarity across the 2 benefits. The price-quantity/price-expenditure relationship for a product or service can be evaluated by measuring the price elasticity—or flexibility—of demand, which compares the change in utilization or expenditures divided by the percentage change in price. Price elasticity values are typically expressed as “the change in the quantity demanded from a 1% increase in price.” For example, a diversity elasticity value of 0.25 for physician office visits means that a 1% increase in distance results in a 0.25% increase in the number of physician office visits; a price elasticity value of -0.25 for physician office visits means that a 1% increase in price results in a 0.25% decrease in the number of physician office visits.

When a product or service is considered to be price elastic, it means that as the price increases, utilization or total expenditure decreases. Price elasticity occurs because there are reasonable substitutes available for that product or service. When no substitutes are available, changes in price are not as likely to impact use or expenditure. The determination that a service is a substitute is based on the cross-price elasticity of demand, which measures the price relationship of service “x” to demand (utilization or expenditures) for service “y.” When the cross-price elasticity of demand is negative, the substitute is considered to be a complement; when positive, the service is considered to be a substitute.

An example of a substitute product can be demonstrated by a consumer’s choice in the purchase of beer. The consumer is indifferent to the brand of beer purchased as long as the price of each brand remains the same. When the price of beer “A” increases and the price of beer “B” is held constant, the consumer will preferentially purchase beer “B.” An example of a pharmaceutical substitute would be the purchase of esomeprazole over the counter (OTC) in lieu of prescription esomeprazole. A complementary product or service would be one in which its use increases with the use of a primary product or service. An example of a complement would be the consumption of beer nuts when drinking beer. When the price of beer increases, the consumption of both beer nuts and beer decreases even though no change occurred in the price of beer nuts. An example of a pharmaceutical complement can be demonstrated by omeprazole OTC and naproxen—as naproxen use increases, the use of omeprazole OTC would also be expected to increase, particularly in persons at increased risk of gastrointestinal bleeding.

Figure 1 illustrates an indifference curve, so called because it identifies points where consumers are indifferent to the purchase of product A or product B because they both provide the same level of utility or satisfaction. A perfect substitute is shown by the negatively sloped dotted line. The solid L-shaped line plots the perfect complementary relationship between product C and product A. In addition to the price of the product or service, the time cost may also play an important role in the decision of which service or product to buy.

The total member cost of a physician office visit includes the copayment amount, the time cost for the member to travel to the physician’s office, and the wait time involved to see the physician. Because of the existence of this noncash form of cost,
However, it did not report types of health care services. These 2 factors—separation of the types of care and consumer behavior when faced with a choice among services acted as a complement.

There is a current trend cross-price relationships, these health insurance benefits are for medical services and prescription drugs logically suggests that introduced a 25% coinsurance payment of total expenditures when there had been no previous coinsurance fee reduced physician office visit use by approximately 25%.

The RAND Health Insurance Experiment characterized consumer behavior as related to the cost for acute care, chronic care, well care, outpatient care, hospital care, total medical and dental care, and prescription drugs. However, it did not report substitutions or complements for these products and services and apparently did not consider combinations of care. Price-related differences in utilization and price elasticities were reported on an aggregate level: (1) Higher cost sharing was associated with lower health care use. (2) No net effect on health was evident for the average patient; however, although counterintuitive, restricted activity days decreased with greater cost sharing. Poor patients showed improved blood pressure control with lower cost sharing as a result of greater compliance due to easier access to medication. (3) Overall expenditure levels did not vary by income group, but the types of services used did vary; poor patients experienced a greater reduction in the use of ambulatory services with increased cost sharing.

O’Brien, who studied National Health Service prescription drug use in the United Kingdom, reported a positive cross-price elasticity between OTC and prescription drugs, meaning that OTC drugs act as a substitute for prescription drugs. Manning et al. evaluated the cross-price elasticity for inpatient versus outpatient services and found that outpatient services were not a substitute for inpatient services, but suggested that outpatient services acted as a complement.

Even though the behavior of the price–quantity relationship for medical services and prescription drugs logically suggests cross-price relationships, these health insurance benefits are commonly considered independently. There is a current trend toward designing and managing prescription drug and medical benefits separately, perhaps without adequate market information about consumer behavior when faced with a choice among types of health care services. These 2 factors—separation of the management of pharmacy and medical benefits and lack of adequate market information about consumer behavior—may have significant cost implications for consumers, employers, and health plans. To address this lack of information, we conducted an observational study of consumer preference for the combination of health care services represented by physician office visits and prescription drugs in a commercially insured population. Consumer preference is the relationship between acquiring products or services and the satisfaction that this acquisition brings to the consumer, which is based on the assumption that consumers will seek the highest level of satisfaction that fits within their budget constraint. Our contention is that the benefit design for physician office visits helps to explain consumer preference for the number and type of prescription drugs used and that the benefit design for prescription drugs helps to explain consumer preference for the number and possibly the type (specialist or primary care) of physician office visits used.

Methods

The drug formulary for the pharmacy benefit for health plan members at BlueCross BlueShield of Tennessee in 2002 and 2003 was defined by a 3-tier copayment design (the drug formulary is no longer available on the Web site, but it may be obtained from the authors). The formulary contained some exclusions such as erectile dysfunction drugs, infertility drugs, antiobesity drugs, smoking deterrents, OTC drugs except insulin and glucose-monitoring products, and investigational drugs except where current Tennessee statute allows for coverage through medical exception (off-label use of drugs in Tennessee Code Title 56, Chapter 7, Part 23 [TCA 56-7-2332]). Copayment tier 1 included all generic drugs listed in the formulary as well as generic drugs that were not listed, with the exception of single-source generic drugs that are produced and priced by a single manufacturer at near-brand price. Copayment tier 2 included only selected brand-name formulary drugs that were considered by the plan to be more cost effective than similar drugs within a particular drug class (e.g., antidepressants, antihypertensives). Copayment tier 3 included brand-name products that were not selected for tier 2 plus all brand-name products that were not listed in the formulary. All brand-name drugs with a generic equivalent were also in tier 3. The copayments for prescription drugs varied by tier, with the lowest copayment in tier 1 and the highest copayment in tier 3.

The pharmacy benefit also included a preauthorization requirement for the following drugs: adapalene, anabolic steroids, fluconazole,itraconazole, palivizumab, thalidomide, tretinoin, antiobesity drugs (benzphetamine, diethylpropion, orlistat, phendimetrazine, phentermine, sibutramine), erectile dysfunction drugs, human growth hormone, and infertility drugs. The 3-tier copayment formulary structure did not change over the 2-year study period, although some drugs changed tiers. For example, Zoloft moved from tier 3 in 2002 to tier 2 in 2003, while Remeron moved from tier 2 to tier 3.

Estimates of price effects on demand (utilization or expenditures) require a price change to reduce the potential for misinterpreting the relationship between price and demand by inappropriately attributing a level of demand to, in this case, price. In our study,
price change was measured by the change in point-of-service, out-of-pocket cost (copayment or coinsurance) from 2002 to 2003 for the study population. The price change is referred to as “exogenous” because our study models used price to estimate demand. Although the consumers did not have the ability to control price, they could control the number of units purchased and the total amount of their expenditures. The magnitude of the price change in our study was not modest, ranging from 49% to just over 350% of the 2002 copayment for the price change cohorts (Table 1).

Each year, approximately 30% of the plan membership renews or initiates their health insurance relationship with BlueCross BlueShield of Tennessee by enrolling with an effective date of January 1; the remaining 70% enroll or renew at other dates throughout the year. Annual renewal and enrollment is frequently accompanied by cost-sharing changes made to suit the objectives of the employer or individual or both based on their preference for how cost is paid, whether through a premium or a point-of-service copayment. Premiums are generally lower when point-of-service cost sharing (copayment or coinsurance) is higher and vice versa. Benefit plans may also fluctuate due to regulation changes from the state department of insurance, legislated mandates, product popularity and market trends, and the strategic and operational objectives of the health plan. At the January 2003 membership renewal, the total number of benefit plans in the study population increased from 48 to 57. Each plan represented a different combination of benefit levels for office visit (copayment and coinsurance) and prescription drug purchases during the 2-year study period; claims for other services were not studied separately but were included in aggregate as total health care expenditures and total plan-paid costs. Total health care expenditures denotes the total amount of money paid per member for medical services and products. Total health care expenditures = member cost share + plan-paid expenditures. Member cost share = copayment, coinsurance, and deductibles. Plan-paid expenditures include any provider payments made by the health plan. The unit of analysis was the member record, comprising aggregated services and costs by member for either 2002 or 2003. Of the total 44,828 members, 13,114 (29.3%) had no physician office visit or prescription drug claims in 2002.

Data were extracted from an internal database that houses all member records and claims for health plan local business. Members from national accounts and the Federal Employees Program, those who were self-insured, those without both medical and prescription drug coverage, and those who were not covered for the entire 2 calendar years were not included in this study. Non-Tennessee residents were excluded.

The potential study population was 123,875 fully insured members from 2002. We included only those members whose benefit year coincided with the calendar year (January 1) for ease of analysis in reporting per-member-per-year (PMPY) expenditures and utilization. The benefit renewal date and any benefit copayment/coinsurance changes would therefore have the same change date, with claims records both 12 months before and after the benefit change being represented. Using these variables, our study population resulted in 44,828 members. The outcome of the extraction design is 2 distinct periods (2002 and 2003) of claims records for the same 44,828 fully insured members, producing a balanced panel. All 44,828 members were enrolled in a preferred provider organization during the study period. No other selection criteria were employed.

Claim records included all physician office visits and prescription drug purchases during the 2-year study period; claims for other services were not studied separately but were included in aggregate as total health care expenditures and total plan-paid costs. Total health care expenditures denotes the total amount of money paid per member for medical services and products. Total health care expenditures = member cost share + plan-paid expenditures. Member cost share = copayment, coinsurance, and deductibles. Plan-paid expenditures include any provider payments made by the health plan. The unit of analysis was the member record, comprising aggregated services and costs by member for either 2002 or 2003. Of the total 44,828 members, 13,114 (29.3%) had no physician office visit or prescription drug claims in 2002.
Demand was measured in 2 ways: (1) utilization, denoting the number of office visits and pharmacy claims PMPY and (2) expenditures, denoting health plan-paid costs PMPY by benefit category. Prescription drug expenditures by tier are depicted in Table 2 as benefit plan-paid costs PMPY. An office visit is defined as a member encounter with a unique physician on a specific date. A consequence of this definition is that more than 1 claim for the same patient from the same physician could be submitted for a specific date, but these claims would be counted as 1 office visit. Claims from a patient visiting 2 different physicians on the same day would be counted as 2 office visits. Total plan expenditures include those for hospital inpatient and outpatient services, freestanding outpatient facilities such as ambulatory surgery centers, physician office and hospital visits, home health, durable medical equipment, home infusion therapy, and specialty and prescription drugs, in addition to other less frequently used products and services.

Our analytic strategy was to estimate demand by using least squares dummy variable (LSDV) regression. LSDV regression is a fixed-effects model specification, which is considered to be

### Table 2: Descriptive Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>2002 Mean [SD]</th>
<th>2003 Mean [SD]</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.8 [17.8]</td>
<td>35.8 [17.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total sample</td>
<td>44,828</td>
<td>44,828</td>
<td>NA</td>
</tr>
<tr>
<td>Females (%)</td>
<td>22,018 [49.1%]</td>
<td>22,018 [49.1%]</td>
<td>NA</td>
</tr>
<tr>
<td>Actual DxCG score</td>
<td>1.17 [3.03]</td>
<td>1.33 [3.4]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCP distance in miles per visit</td>
<td>23.7 [38.1]</td>
<td>23.3 [36.5]</td>
<td>0.337</td>
</tr>
<tr>
<td>PCP distance in miles per visit</td>
<td>9.95 [15.2]</td>
<td>9.57 [12.9]</td>
<td>0.002</td>
</tr>
<tr>
<td>OV copayment ($)</td>
<td>11.75 [21.31]</td>
<td>12.12 [22.50]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-1 copayment ($)</td>
<td>7.14 [5.37]</td>
<td>7.37 [4.07]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-2 copayment ($)</td>
<td>22.36 [23.70]</td>
<td>23.32 [27.02]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-3 copayment ($)</td>
<td>24.59 [28.36]</td>
<td>26.56 [34.88]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Per Member per Year Measures**

<table>
<thead>
<tr>
<th></th>
<th>2002 Mean [SD]</th>
<th>2003 Mean [SD]</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCP office visits†</td>
<td>2.3 [4.9]</td>
<td>2.5 [5.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCP office visits†</td>
<td>2.1 [3.2]</td>
<td>2.2 [3.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-1 pharmacy claims</td>
<td>3.7 [7.2]</td>
<td>4.4 [8.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-2 pharmacy claims</td>
<td>3.6 [7.2]</td>
<td>4.0 [7.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-3 pharmacy claims</td>
<td>2.7 [5.5]</td>
<td>2.8 [5.7]</td>
<td>0.001</td>
</tr>
<tr>
<td>Total pharmacy claims</td>
<td>11.07</td>
<td>12.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCP office visit expenditures ($)</td>
<td>133.69 [224.85]</td>
<td>142.17 [234.47]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCP office visit expenditures ($)</td>
<td>252.83 [1,093.86]</td>
<td>309.17 [1,662.18]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total physician office visit expenditures ($)</td>
<td>386.52</td>
<td>451.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-1 pharmacy expenditures ($)</td>
<td>41.51 [143.42]</td>
<td>52.97 [170.09]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-2 pharmacy expenditures ($)</td>
<td>176.15 [614.57]</td>
<td>218.16 [720.14]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tier-3 pharmacy expenditures ($)</td>
<td>146.78 [1,078.67]</td>
<td>176.86 [1,267.44]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total pharmacy expenditures ($)</td>
<td>390.55</td>
<td>478.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total plan-paid expenditures ($)§</td>
<td>1,766.49 [5,676.13]</td>
<td>2,092.26 [6,828.78]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* For the study sample of 44,828 members.
† PCP and SCP office visit expenditures include plan-paid expenditures for all services, including laboratory and radiology received by the patient in the course of the visit; however, it specifically excludes surgery, high-technology imaging such as MRI, PET, and CAT scans; invasive diagnostic procedures such as colonoscopy and bronchoscopy.
‡ Student t test.
§ Total plan-paid health care expenditures represent expenditures for all benefits paid by the health plan, including hospital inpatient and outpatient services, physician and other professional services, prescription drug and home infusion therapy, durable medical equipment, and home health and medical supplies.
DxCG = diagnostic cost group; PCP = primary care physician; SCP = specialty care physician.
more appropriate when the principal focus within the sample studied is in the effects themselves, as was the case in our analysis.\textsuperscript{23} Fixed-effects models are useful when the samples are not randomly drawn, as in our study. They are also known as unobserved effects models because they are able to account for unobserved effects that are constant, and those vary over time.\textsuperscript{24}

Separate regression analysis was conducted to model utilization and expenditures by benefit category. The 5 utilization benefit categories modeled were primary care physician (PCP) office visit PMPY, specialty care physician (SCP) office visit PMPY, tier-1 prescriptions PMPY, tier-2 prescriptions PMPY, and tier-3 prescriptions PMPY. The 5 expenditure benefit categories modeled were PCP $PMPY, SCP $PMPY, tier-1 prescription $PMPY, tier-2 prescription $PMPY, and tier-3 prescription $PMPY. We selected these benefit categories because they represent, on average, the most typical components of the

### TABLE 3 The Empirical Model

The theoretical model for measuring price elasticity begins with the linear demand model\textsuperscript{17}:

$$Q_d = a - bP$$

where $Q_d$ = quantity demanded, $P$ = price, $a$ = the quantity demanded when price = 0 (the quantity axis intercept), and $b = P/Q$ or the slope of price-quantity, which is required by the law of demand to be negative. From this basic demand model, we take the derivative of quantity with respect to price (marginal function):

$$\frac{dQ_d}{dP} = -b$$

Next, the average function is calculated:

$$\frac{Q_d}{P} = \frac{a - bP}{P}$$

Finally, the ratio of the marginal function to the average function is taken:

$$\frac{-bP}{a - bP} = E_d$$

where $E_d$ is the price elasticity of demand.

The calculation is simplified by using the natural log transformation:

$$E_d = \frac{d(lnQ_d)}{d(lnP)}$$

As is common with large data sets, this is accomplished by transforming the variables by taking the natural logarithm for all but dummy variables and then applying the ordinary least squares regression method to the transformed variables (log-log model). The functional form of the regression model for elasticities is specified by Gujarati\textsuperscript{14} below:

$$ln Y_j = ln \beta_1 + \beta_2 ln X_j + u_i$$

An additional feature of the log-log model is that the log transform will also have the effect of transforming an exponential relationship to a linear one. Deaton and Muellbauer\textsuperscript{15} base the price elasticity of demand in the budget constraint by equating total expenditures to the sum of all prices for all purchases multiplied by the quantities for all purchases. Concerning health insurance benefits, in which total expenditures are likely to be related to the benefit design and the amount of the monthly premium, the traditional total expenditure constraint is not as important. The well-known economist, Milton Friedman,\textsuperscript{20} describes the reduced importance of the health care expenditure constraint: “Two simple observations are key to explaining both the high level of spending on medical care and the dissatisfaction with that spending. The first is that most payments to physicians or hospitals or other caregivers for medical care are made not by the patient but by a third party—an insurance company or employer or governmental body. The second is that nobody spends somebody else’s money as wisely or as frugally as he spends his own.” Such items as government-mandated benefits imposed by state legislatures,\textsuperscript{22,23} leverage,\textsuperscript{24} monopoly pricing, information asymmetry,\textsuperscript{25} and health care capacity\textsuperscript{26} are more important determinants of total health care expenditures than the traditional budget constraint construct. Leverage is the effect of reducing the consumer point-of-service out-of-pocket exposure compared with the prices of health care products or services. Increasing leverage results in premium increases due to the effect of the relative exposure change on plan-paid costs.

The following equation presents the Deaton and Muellbauer\textsuperscript{15} specification:

$$log q_i = \alpha + \epsilon \log x + \sum h \log p + u_i$$

where $log = \text{natural log}$, $\alpha$ is the intercept term shown previously as $\beta_1$, $h$ represents products that are closely associated with the study product, $x$ represents total expenditures, $p$ = price, and $e$ represents elasticity. An important assumption of this approach is that the only role of price and total expenditures is to represent elasticity. An important assumption of this approach is that the only role of price and total expenditures is to represent elasticity. An important assumption of this approach is that the only role of price and total expenditures is to represent elasticity.
average medical care bundle of products. In our model, expenditures (health plan-paid costs) are those costs that the health plan is contracted to pay to the provider after subtracting the out-of-pocket costs paid at the point of service by the insured member.

The specification of the empirical model (Table 3) used in our analysis is the typical LSDV model:

\[ \ln Y_i = \alpha_1 + \alpha_2 D + \alpha_3 D_k + \beta_1 \ln X_{ij} + \ldots + \gamma_1 (D_k \ln X_{kj}) + \ldots Z_i + u_i \]

where \( i \) indexes individuals, \( y \) is a continuous variable estimating either units or expenditures for each benefit category in separate regressions, \( \alpha_1 \) is the intercept, and \( D \) is a dummy variable that represents the year (0 for 2002 before the benefits changed, 1 for 2003 after the benefits changed). The addition of \( D \) as an independent variable creates a differential intercept, representing the change in 2003 from the 2002 value of the intercept. The multiplication of the study variable slope terms by \( D \) creates differential slope terms that show the change from 2002 to 2003.

\( \beta \) is used to represent the coefficient for the slope (\( X \)) terms and \( \gamma \) the coefficient for the differential slope terms. \( \beta \) values exist for each study and control variable, and \( \gamma \) values exist for each copayment and distance variable.

Study variables, represented by \( k \), included office visit copayment (expressed in dollars) coinsurance payment (expressed in percentage of contractual amounts), tier-1 pharmacy copayment, tier-2 pharmacy copayment, and distance in miles from the member’s home address to PCP and SCP offices. Distance was measured using the Ingenix, GeoAccess GeoNetworks system. Distance, while perhaps the best measure available, is imperfect because of provider selection based on proximity to work or school rather than residence. Differential slopes are included for office visit copayment and coinsurance payment, as well as tier-1, tier-2, and tier-3 pharmacy copayments. Differential intercepts are also included for member cohorts whose copayment or travel distance changed from 2002 to 2003 by benefit category.

\[ Z \] is an array of control variables that includes age, gender, the diagnostic cost group (DxCG) prospective relative risk score, and member geographical region of residence. The DxCG score represents the next year’s expected total health care expenditures and is commonly used for risk adjustment and predictive modeling. Copayment and coinsurance are measures of price representing the out-of-pocket expenditures incurred by the member for the purchase of the benefit product or service. Price effects are measured only by differential coefficients, denoted by \( D \), because they reflect the change in utilization or expenditures associated with the price change as well as the member cohorts that experienced a price change, denoted by \( g \).

We used this empirical model to test the hypothesis that the demand for physician office visits and prescription drugs is related by complementarity or substitutability, which are cross-
relationship of the use and costs of physician office visits and prescription drugs to travel distance and increases in member cost share

Mas-Colell et al. graphically analyzed the demand for a product as a function of its price and the price of a related product. Their simple illustration clearly shows the importance of understanding the role of cross-price information, although it does not address any of the technical methodological aspects of such an analysis. Similar simple illustrations are represented in Figures 2 and 3. Figure 2 shows the best-fit lines from a 2-variable linear regression between the distance traveled to the SCP's office—in this case, an opportunity cost—and the PCP's office visits PMPY. There is a separate regression line for each tier-3 prescription copayment level in the study sample. The Chow test demonstrates that the plotted regressions are different (F = 7.574, F(2,25) = 5.57, β = 0.01). The adjusted R² (coefficient of determination) is 0.86 for the $20.00 copayment, 0.98 for the $35.00 copayment, 0.85 for the $50.00 copayment, and 0.84 for the pooled regression. Figure 3 shows the best-fit lines from a 2-variable regression where x = tier-1 prescriptions PMPY and y = the distance to the specialist's office. Separate best-fit lines are plotted for each office visit copayment level. The Chow test also shows that the models are different (F = 16.856, F(2,34) = 5.26, β = 0.01). The adjusted R²s are 0.91, 0.97, 0.88, and 0.79 for the $10.00, $15.00, $20.00, and $25.00 copayments, respectively, and 0.71 for the pooled regression. Figure 2 demonstrates prices or costs for 2 different products and their relationship to yet a third product, the PCP office visit. Figure 3 also depicts prices or costs for 2 different products and their relationship to a third product, tier-1 prescriptions.

The study sample included 44,828 commercially insured members from 2002 who were monitored for 12 months in calendar year 2003 after benefit categories were changed. Table 1 reports the sample size of the study population cohorts who had copayment or distance changes as well as the average amount of change for each affected benefit level. Of the 44,828 members, 11.3% (5,066) had coinsurance cost-sharing requirements: 10.4% had coinsurance alone, while 0.9% had both coinsurance and fixed copayments.

Descriptive statistics for the study population are shown in Table 2. All variables except the distance to a specialist's office and sample size were significantly different in 2003 compared with 2002. Control variables were used to account for observable differences in member characteristics. We controlled for differences between members associated with residence by geographical region of the state, age, gender, and expected health care costs via the DxCG score. Other differences between members were not observed including income, race, and educational level, among others.

price elasticities with opposite signs. Our hypothesis would be rejected if, for all models, no cross-price elasticities were significant (results for own-price and cross-price elasticities are shown in Table 4). Our a priori significance level was P < 0.05. Since a physician visit is not required to provide a new prescription drug to an established patient, physician visits did not need to be eliminated from the data set to accommodate the measure of cross-price elasticity. Rather, eliminating office visits under such a scenario would reduce the ability to identify complementarity between office visits and prescription drugs where it existed. The focus of our study was to determine whether a relationship exists between benefit categories on the basis of price and time costs. Therefore, we were not concerned with a specific drug, drug class, or disease state, but with the benefit categories themselves as defined by price (copayment and coinsurance) and distance.
The LSDV regression utilization model results are shown in Table 4. The differential study variables demonstrate the price–quantity/price–expenditure relationship within members both before and after a price change, thus measuring the effects of the price change that occurred on January 1, 2003, when the payment increase went into effect. Because office visit coinsurance was used in only 11.3% of the study population and did not show significant variation, it was dropped from all models. The OV benefit design was exactly the same for both PCPs and SCPs in both 2002 and 2003, which prevented using office visit copayment as a means of identifying the relationship between primary care visits and specialist visits, as no cross-price elasticity can be determined.

**Distance Effects**

We anticipated using distance as a proxy for the time cost of an office visit. Our a priori assumption was that distance would be inversely related to the number of visits. However, we found that distance was directly related to the number of office visits. Positive distance elasticities for office visits may represent the consumer's perception of value and perhaps quality—as the distance to a physician's office increases, the value of the physician's services is perceived to be greater. While not implying that we have tested this assumption, Table 5 presents the number of office visits by quintile of distance for both PCPs and SCPs and demonstrates that office visits generally increased with distance. When the distance to a PCP office visit was lower (i.e., perhaps the perceived value of a PCP office visit was less), an increased number of SCP office visits were used. When the distance to an SCP office was higher (the perceived value was greater), an increased number of SCP office visits were used. As shown in Table 4, all significant distance elasticities are positive, indicating that a greater travel distance is associated with an increase in office visit utilization/expenditures or pharmacy utilization/expenditures.

**Price Effects**

Table 4 illustrates the price elasticity results for all models. Price elasticity values are expressed as the change in the quantity demanded from a 1% increase in price. The PCP office-visit model displayed a significant negative cross-price elasticity for tier-1 prescriptions, indicating that tier-1 drugs are a complement to PCP visits. A 1% increase in the tier-1 copayment was associated with a 0.118% decrease in PCP office visits. Tier-1 and tier-3 prescription drugs showed significant positive cross-price elasticities. Higher tier-1 and tier-3 copayments were associated with higher SCP expenditures (substitute), while higher tier-2 copayments were associated with lower SCP expenditures (complement). Higher tier-1 and tier-3 copayments were associated with higher SCP expenditures (substitute), while higher tier-2 copayments were associated with lower SCP expenditures (complement). Higher tier-1 and tier-3 copayments were associated with higher tier-2 expenditures, suggesting that tier-2 drugs are a substitute for both tier-1 and tier-3 prescription drugs. Neither tier-1 nor tier-3 expenditures showed significant cross-price elasticities. Own-price elasticities were significant for all prescription drug expenditures and tier-3 prescription drug utilization. Increased office visit and tier-2 copayments were associated with lower total plan-paid expenditures.

**Discussion**

Our study adds to the current literature on pharmacy benefit design by determining that a significant relationship exists between physician office visit utilization and prescription drug purchases on the basis of cost sharing and that the distance to a physician’s office is directly, not inversely, related to the number of office visits utilized. Our data reflect consumer preferences for particular aspects of the 5 most common products or services paid for by health insurance companies. These results compare with numerous previous studies that also found own-price elasticities for both physician services and prescription drug use based on cost sharing that fell within the same statistical ranges as those from our study. Acton and Coffey investigated distance and time elasticities, respectively, with respect to physician office visits, and their results also give credence to our conclusions (discussed below).

### Table 5: Relationship Between Average Frequency of Office Visits and Average Distance in Miles

<table>
<thead>
<tr>
<th>Distance Quintile</th>
<th>PCP Distance</th>
<th>PCP Visits PMPY</th>
<th>SCP Distance</th>
<th>SCP Visits PMPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.61</td>
<td>3.41</td>
<td>3.00</td>
<td>3.80</td>
</tr>
<tr>
<td>2</td>
<td>3.91</td>
<td>3.55</td>
<td>7.01</td>
<td>4.52</td>
</tr>
<tr>
<td>3</td>
<td>6.63</td>
<td>3.56</td>
<td>11.74</td>
<td>4.73</td>
</tr>
<tr>
<td>4</td>
<td>10.61</td>
<td>3.52</td>
<td>21.12</td>
<td>4.72</td>
</tr>
<tr>
<td>5</td>
<td>25.99</td>
<td>3.70</td>
<td>74.57</td>
<td>5.00</td>
</tr>
</tbody>
</table>

* n=8,966 in each quintile.

PCP=primary care physician; PMPY=per member per year; SCP=specialty care physician.
When uncertain, price or cost can be a signal of quality to consumers. Historically, there has been a lack of market information about the quality of health care providers, leading to consumer uncertainty regarding the purchase decision. When the price factor remains constant due to fixed office visit copayments, the distance to a physician’s office may be a proxy for the perceived quality of services. Our results demonstrated that office visit and prescription drug benefits are related by copayment and distance elasticity. All prescription drug use was higher when the distance to a specialist was greater.

The price increase was related to behavioral changes in members. Tier-2 prescription utilization and total expenditures decreased when the office visit copayment amount increased; thus, tier-2 prescriptions are a complement to office visits. These price effects occurred following significant benefit price changes, suggesting that office visit copayments could be a significant factor in predicting prescription drug use. Based on the positive cross-price elasticities of PCP and SCP expenditures and SCP utilization, tier-3 prescriptions can be seen as a substitute for office visits. A prescription drug is frequently an output of a physician office visit. In our study, that output was likely to be a tier-1 or tier-2 prescription for PCP office visits or a tier-2 prescription for SCP office visits. A prescription drug is also frequently the output of a telephone call to the physician rather than the result of an office visit; in our study, that output was likely to be a tier-1 or tier-3 prescription. By reducing the need for an office visit, the phone call created the opportunity for a prescription drug to substitute for an office visit.

By studying nonmonetary factors in health care demand, Acton reported positive distance elasticities for physician office visits. He imputed distance by travel mode, which was modeled using dummy variables. Concerning physician office visits, Acton concluded that those who walked to the physician’s office (least distance) demanded the fewest visits and those who traveled by bus, subway, or taxi had similar demand levels. One reasonable interpretation of Acton’s findings is that those who travel further for physician office visits demand relatively more visits, which is comparable with the findings in our study.

Coffey investigated the role of time elasticities in the initial demand for physician office visits and choice of provider, finding that a high expected time cost had a negative effect on both the choice of provider and initiation of the demand for provider office visits but did not influence the number of visits demanded once care had been established. Coffey did not report distance elasticities; however, both Acton and Coffey justified their findings by proposing that, as out-of-pocket costs declined, factors other than price became more important in the purchase decision. Acton’s analysis was published in 1975 and Coffey’s in 1983, when the average out-of-pocket share of personal health care expenditures was 33% and 25%, respectively, and 75% and 60% for prescription drugs, respectively. In 2004, the average out-of-pocket share of personal health care expenditures was 15.1%; it was 24.9% for prescription drugs.

Cost sharing in the health insurance benefit design has previously been reported to have an effect on physician service utilization. Rosett and Huang aggregated physician and hospital service together as medical care and reported the price elasticity for medical care as ranging from -0.35 to -1.5. Fuchs and Kramer reported price elasticities for physician services of -0.1 to -0.36. Phelps and Newhouse reported an arc price elasticity of demand for physician visits of -0.137. Manning et al. reported price elasticities in the -0.1 to -0.2 range. Wedig reported elasticities of -0.032 to -0.16, depending on whether the model was use/nonuse or conditional on use. Our study reported office visit own-price elasticities of -0.081 and -0.076 for expenditures and -0.067 for utilization, results that are slightly smaller but similar to the other estimates discussed above.

Important distinctions among these previous studies are the price measure, the level of utilization aggregation or expenditures, and the time periods studied. Wedig was not able to observe the prices in effect for those who did not utilize the service. Rosett and Huang did not use direct measures of price and use. Fuchs and Kramer used the average and net prices of those who utilized the services; nonutilizers did not know the price, that is, their decision not to purchase was not based on the monetary price. In our study, price was observable for both the utilizing and nonutilizing population segments.

The nature of the price measures in the above-mentioned studies included coinsurance rates and out-of-pocket costs measured as a ratio of total care received, in addition to average rates based on aggregates or estimates. A copayment price measure is a more explicit price signal than coinsurance. Coinsurance in the current market is a percentage of a negotiated fee schedule. However, in some of the previous studies, coinsurance was applied to a usual and customary fee and, in at least one instance, to a discounted usual and customary fee. Because there is more explicit price information revealed in the copayment fee, it is possible that the cost signal to the consumer could result in a different price effect.

Contoyannis investigated the price elasticity for prescription drugs, reporting elasticities between -0.12 and -0.14. The RAND Health Insurance Experiment found the elasticity for prescription drug expenditures to be -0.27. Coulson estimated the price elasticity of prescription drug use in low-income Pennsylvanians at -0.34. Harris reported a price elasticity pertaining to all prescription drug use of -0.11 following copayments increases. Hughes reported both long- (0.37) and short-term (-0.32) elasticities of prescription drug use following a copayment change. Johnson reported that the price elasticity of prescription drug use varied from -0.01 for copayments between $1.00 and $3.00 to -0.12 for copayments between $3.00 and $5.00 but stated that there were no differences in physician office visit utilization or hospitalizations. Smith reported cross-sectional price elasticity for the number of size-
adjusted prescriptions at -0.098. The previous studies did not separate prescription drugs by benefit tier. Meissner et al. studied the effect of rising copayment levels on the use of low-sedating antihistamines and nasal steroids and found that the arc price (own-price) elasticity of demand was 0.39 and -0.22, respectively. The Meissner results are different in sign (±) but similar in magnitude to the own-price elasticities reported in our study. Important methodological differences exist between our study and Meissner's that could account for the differences observed, including the bases of the price-elasticity estimate models, the inclusion of cross-prices, and distance information.

Limitations
A limitation of the fixed-effects model is that interpretation of the results is conditional. A lack of segregation in the copayment amount between PCP and SCP office visits limited our ability to identify the precise nature of the cross-price relationship, thereby resulting in an ambiguous result. It also seems unlikely that this consumer bundle of 5 products and services, the 5 most common products and services paid for by health insurance companies, fully represented the average medical care bundle; the presence of other products or services in the analysis, such as OTC drugs and emergency room visits, could yield a different interpretation of results or different results. Income, education, and race were not considered in this study. Income, education, and race were not considered in this study. The role of Internet-mediated health information was not available nor considered in this study and may be a substitute for physician office visits for information seekers.  We also used pharmacy claims rather than days supply as the measure of pharmacy utilization and did not investigate the possible effect of mail-service pharmacy in 2003 versus 2002.

Conclusions
The results of the present study support our hypothesis that a relationship exists between the use of physician office visits and the type/tier of prescription medication purchased based on expenditure and travel-time factors. A 1% increase in the office visit copayment was associated with a 0.105% reduction in the use of tier-2 drugs. A 1% increase in tier-1 pharmacy benefit copayments was associated with lower PCP office visits and expenditures and higher SCP office visits and expenditures. An increase in the tier-2 pharmacy benefit copayments was associated with lower PCP and SCP expenditures; an increase in the tier-3 copayment was associated with higher PCP and SCP expenditures as well as SCP office visit utilization. The principal health plan policy implications of our research are that medical benefits and pharmacy benefits are more likely to be optimally managed in concert rather than as 2 independent benefits. When pharmacy benefits are incorporated into the management of other medical services (office visits), it is then possible to consider and adapt to cross-price effects. Further investigations of complementarity and substitutability that contain a broader variance in price changes for the bundle of products and services in our analysis could be clarifying for the health insurance industry.

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Prevalence of Drug-Related Problems and Cost-Savings Opportunities in Medicaid High Utilizers Identified by a Pharmacist-Run Drug Regimen Review Center

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ABSTRACT

BACKGROUND: Despite numerous reports of state Medicaid drug utilization review (DUR) programs, little data are available about the prevalence of drug-related problems (DRPs) in Medicaid patients. A university-based, pharmacist-run DUR program for high utilizers was created as an alternative to imposition of a statutory limit of 7 medications per month in the Utah Medicaid program in 2002. The DUR program was designed to suggest ways that high-utilizing patients could decrease their total number of medications to 7 or fewer prior to imposition of the 7-medication limit at some time in the future.

OBJECTIVE: To describe the experience in 1 Medicaid DUR program and to report the prevalence of DRPs and cost-saving opportunities (CSOs) among a population of Medicaid recipients who were high utilizers of prescription drugs.

METHODS: DRPs were identified by 5 clinical pharmacists employed by the Drug Regimen Review Center (DRRC) in Salt Lake City. The purpose of the center was to provide drug therapy review services for a select number of Utah Medicaid recipients (200-300 per month) who exceeded a 7-medication limit during the calendar years 2003 and 2004.

RESULTS: Out of 391,890 eligible Medicaid recipients, 242,411 (62%) received at least 1 medication, and 16,958 (4.3%) exceeded the 7-medication limit during the review period. Of those exceeding the limit, the DRRC reviewed a total of 3,706 (21.9%) patients, representing the highest utilizers by volume of medication. The prevalence of DRPs considered clinically important in the review cohort was 79.7% of patients, including therapeutic duplications in 54.6% of patients, dose form optimization in 29.7%, and inappropriate uncoordinated care in 25.3%. The average pharmacy cost per month for patients with at least 1 DRP was $1,081; by contrast, the average pharmacy cost per month for all other patients receiving at least 1 prescription was $91.

CONCLUSIONS: Approximately 4% of Medicaid recipients exceeded the 7-medication monthly limit. Among the 22% highest utilizers in this group, 48% of nursing home residents and 87% of ambulatory recipients had at least 1 DRP, or an overall rate of 80% of high-use Medicaid recipients or as much as 3.2% of the Medicaid population.

KEYWORDS: Medicaid, Drug utilization review, Drug-related problems, Therapeutic duplications, Health policy

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STATES have been required to implement both prospective and retrospective drug utilization review (DUR) programs for ambulatory Medicaid recipients since 1993, as part of the changes required by the Omnibus Budget Reconciliation Act (OBRA) in 1990. Since that time, retrospective DUR programs have been conducted and evaluated in many states, including Texas, Connecticut, Washington, New York, and Wisconsin. Most of these evaluations address interventions surrounding a single specific recommendation or drug-related problem (DRP) and rarely address multiple DRPs in any intervention. Consequently, little data are available about the prevalence of DRPs among Medicaid populations.

One study evaluated whether the rate of DRPs changed among Medicaid patients in 6 states following the OBRA mandate, but the authors did not report the prevalence rates found in their analyses. Authors of an analysis conducted among Medicaid patients in Maryland, Iowa, Washington, and Georgia reported high rates of duplicative therapies, inappropriate dosages, inappropriate durations of therapy, and contraindications. However, these data were reported only for elderly patients (aged 265 years) and only with respect to 5 predetermined DRPs in 8 drug categories. Another study among New York State Medicaid patients evaluated antiretroviral therapy, finding that 44% of patients had suboptimal antiretroviral therapy according to best-practice guidelines.

Previous studies that have examined DRPs have used various criteria for categorizing a patient's drug regimen as problematic. Two studies have used practice guidelines for specific disease states, and 2 have used criteria developed by experts from the University of Maryland and the Philadelphia College of Pharmacy and Science. Another study used criteria from a commercial DUR software program used by 6 state Medicaid programs. Many other investigators have created their own criteria on the basis of clinical judgment and literature review.

In all of the prior evaluations, it appears that pharmacy claims were screened by the programming of querytable databases to identify patients who met the specific criteria established for each DRP. It is unclear whether the prevalence of DRPs identified in this manner would differ from the prevalence that would be found if the DRPs were identified by clinical pharmacists with access to a patient's entire drug regimen and diagnoses. The purpose of our study was to estimate the prevalence of DRPs among Medicaid high utilizers of pharmacy benefits as
Dr. Marcia A. Stewart, PharmD, BCPS, FASCP

Prevalence of Drug-Related Problems and Cost-Savings Opportunities in Medicaid High Utilizers Identified by a Pharmacist-Run Drug Regimen Review Center

**TABLE 1**

<table>
<thead>
<tr>
<th>Drug-Related Problem Category</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
</table>
| Additive toxicity             | The concomitant use of medications with similar pharmacodynamic actions that may produce excessive pharmacologic or toxic effects when given together. Subtherapeutic dosing may lead to adverse effects that cause a given toxicity. | This patient received multiple medications with anticholinergic effects, including amitriptyline, hyoscyamine, diphenhydramine, and promethazine. This may result in an increased risk of anticholinergic toxicity (confusion, dry mucous membranes, blurred vision, urinary retention, or sedation). This patient received multiple medications that may prolong the QT interval, including thioridazine, ziprazidon, amitriptyline, and erythromycin. Adverse cardiac effects (QT prolongation, torsades de pointes, cardiac arrest) could result.

| Dose exceeds usual recommendations | The use of a medication above the recommended dosage range for a patient's age or condition. Subtherapeutic dosing may lead to adverse effects such as hypokalemia and a rise in plasma cholesterol. | This patient received hydrochlorothiazide 50 mg daily to treat hypertension. Doses greater than 25 mg daily usually provide little additional antihypertensive effect yet significantly increase the incidence of adverse effects. This patient received verapamil extended-release at a dose of 450 mg daily. The maximum recommended daily dose for outpatients is 225 mg daily. Higher doses are associated with an increased risk of adverse effects such as hypotension.

| Drug-disease interaction | The use of a medication that is contraindicated due to the patient's age, gender, or disease state(s). | This patient received sumatriptan, a triptan migraine-abortive agent, and has a diagnosis of ischemic heart disease. Use of triptans in patients with ischemic heart disease is contraindicated due to increased risk of adverse cardiac events such as myocardial infarction. This patient has a seizure disorder and received bupropion. Of available antidepressants, bupropion has the greatest propensity to lower the seizure threshold and is not generally recommended for use in patients with a history of seizures.

| Drug-drug interaction | Increased toxicity or decreased therapeutic activity of 1 or more medications due to the concomitant use of another drug that affects its activity. Drugs that induce or inhibit hepatic metabolism, drugs that are highly protein-bound, or drugs that affect the renal clearance of another are frequently involved in drug-drug interactions. | This patient received theophylline and ciprofloxacin. This could lead to increased theophylline serum levels and theophylline toxicity through inhibition of cytochrome p450 enzymes by ciprofloxacin. This patient received an epinephrine auto-injector and a nonselective beta-blocker, propranolol. Use of nonselective beta-blockers should be avoided in patients who are prescribed epinephrine for use in the case of an anaphylactic reaction. Nonselective beta-blockade may cause resistance to epinephrine in anaphylaxis.

| Duration of therapy exceeds usual recommendations | The use of a medication for longer than recommended for the patient's age or condition. Excessive duration of therapy may lead to additional adverse effects and toxicity. | This patient received atorvastatin continuously for 3 months. Atorvastatin is a skeletal muscle relaxant indicated for short-term use in acute musculoskeletal conditions; long-term use may result in tolerance to muscle relaxant effects and physical or psychological dependence. This patient received monthly treatment with acyclovir ointment for 5 months. Acyclovir ointment is indicated only for the initial episode of genital herpes. Clinical trials have shown it to be ineffective in treating recurrent herpes outbreaks.

| Inappropriate uncoordinated care | The prescribing of multiple medications for the same disease state by multiple providers. Uncoordinated care may result in insufficient monitoring of a patient's disease states and could lead to other drug-related problems, such as drug-drug interactions, drug-disease interactions, and therapeutic duplications. | This patient received hydrocodone/acetaminophen opioid analgesics from 2 prescribers at different practice sites. This patient received hydrocodone/acetaminophen opioid analgesics from different prescribers on 3 different days. This patient received multiple medications at 2 different dosages. This patient received 2 different dosages of hydrocodone/acetaminophen opioid analgesics. This patient received psychiatric medications, including paroxetine, quetiapine, and lithium, from 3 prescribers at different practice sites.

| Dose form not optimized | The use of more tablets or capsules than necessary to achieve a desired dose or the receipt of separate dosage forms for 2 agents that are available in a combination product. Streamlining therapy could result in improved patient compliance and clinical outcomes. | This patient received separate dosage forms of albuterol and ipratropium for inhalation. These 2 medications are available in a combination product, albuterol/ipratropium (Combivent). This patient received oral methadone and oral naltrexone for opioid dependence. This patient received 2 different methadone formulations.

| Subtherapeutic dose | The use of a medication below the recommended dosage range for the patient's age or condition. Subtherapeutic dosing may cause patients to experience adverse effects without therapeutic benefit, or may require the addition of other medications to control a disease state that could be controlled by the use of a single medication at an appropriate dosage-level. | This patient received quetiapine 25 mg daily. The usual dosage range for schizophrenia or bipolar mania is 150 mg to 800 mg daily. This patient received acyclovir 200 mg daily for 7 months. The dose range for chronic suppression of genital herpes or herpes labialis is 500 mg to 1,000 mg daily. This patient received valacyclovir 500 mg twice daily for 7 days.

| Therapeutic duplication | The inappropriate use of multiple medications for the same indication. | This patient received 2 different selective serotonin reuptake inhibitors, including paroxetine and citalopram for more than 1 year. This patient received 2 different antidepressants.

| Treatment without an indication | The use of a medication without an apparent indication. Unnecessary exposure to medications may lead to increased risks of adverse events and toxicity. | This patient received a potassium supplement at a dose of 60 mEq daily but did not have a potassium-wasting diuretic or a diagnosis of hypokalemia. This patient has received 3 albuterol inhalers each month, exceeding the usual dosing recommendation of 1 inhaler every 25 days. This indicates uncontrolled asthma; however, the patient did not receive an inhaled corticosteroid as recommended for all patients with mild to severe asthma. This patient has a diagnosis of heart failure but did not receive a beta-blocker. Beta-blockers are generally recommended for patients with heart failure because they have been shown to reduce morbidity and mortality in this population.

| Untreated indication | The absence of a medication that appears to be needed based on usual best practice or guidelines. Untreated indications could result in morbidity and mortality for a patient. | This patient was not prescribed lipid-lowering medications.

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**Notes:**

- DRP—drug-related problem.
- JMCP—Journal of Managed Care Pharmacy.

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identified by clinically trained pharmacists reviewing monthly drug regimens of patients.

**Methods**

The Utah legislature in 2001 authorized a limit on the number of medications per Medicaid recipient per month. In early 2002, Medicaid recipients in Utah were subject to a maximum of 7 medications per month. Several classes of medications were categorized as exempt from this limit. Exempted drug classes included antibiotics, HIV antiviral agents, medications indicated for many chronic conditions such as diabetes and hypertension, among others.

Implementation of the 7-medication limit was short-lived, rescinded in the same month that it was implemented, in February 2002, due to outspoken concerns from patient advocates about the limit's potential to adversely impact the health of patients with multiple disease states. Instead, an agreement was reached between the Utah Department of Health and the University of Utah College of Pharmacy to have clinically trained pharmacists review the drug regimens of patients exceeding 7 nonexempt medications in any month.

All pharmacist reviewers hired for this task were licensed in the state of Utah and had completed a PharmD program in which they received broad training in a variety of clinical settings, including ambulatory care. Three pharmacists had additional residency or fellowship training, and 2 pharmacists had extensive (10-15 years) experience in geriatrics and long-term care. Pharmacist reviewers participated in ongoing discussions to achieve consistency in evaluations. They also voluntarily participated in an ongoing American College of Clinical Pharmacy continuing-education program. Therapeutic areas relevant to our patient population were selected and modules in each therapeutic area were reviewed, after which pharmacists participated in a discussion forum about the module and completed exams. All pharmacists are expected to work toward board certification.

Predetermined categories of DRPs for reviewers were defined before implementation of the program (Table 1). The primary goal of the program was to improve utilization of prescription drugs and to positively impact the health of Medicaid recipients. Consequently, most of the DRP categories included problems considered by reviewers to be clinically important. A secondary goal of the program was to reduce prescription drug expenditures and the number of nonexempt medications among the reviewed population. Therefore, other categories that focused on cost-savings opportunities (CSOs) were also established; they are summarized in Table 2. Reviewers also noted and addressed other drug-therapy concerns if identified.

Reviewers used their clinical judgment to determine whether a patient's therapeutic regimen appeared to be appropriate, based on age, medical conditions, and concurrent drug therapy. For example, if a patient had received 2 different selective serotonin reuptake inhibitors (SSRIs) within a given month, reviewers looked at prior months to determine if it represented duplicative therapy from one or more prescribers or if the patient was switching from one agent to another. Reviewers assessed information obtained from complete pharmacy claims data provided by the Utah State Department of Health Care Finance and the University of Utah College of Pharmacy to have clinically trained pharmacists review the drug regimens of patients exceeding 7 nonexempt medications in any month.

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### Table 2: Cost-Savings-Related Recommendations

<table>
<thead>
<tr>
<th>Drug-Related Problem Category</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name dispensed</strong></td>
<td>The use of a brand-name medication when a less costly bioequivalent alternative is available</td>
<td>This patient received the brand-name loratadine. This drug is now available as a generic and is covered by Medicaid. This patient received the brand-name sustained-release oxycodone. This drug is now available as a generic and is covered by Medicaid.</td>
</tr>
<tr>
<td><strong>Consider alternative</strong></td>
<td>The use of a medication with no bioequivalent generic but with a less costly alternative agent in the same class. For some medications, different agents within the same class are therapeutically interchangeable, and another drug can be selected without negatively impacting the patient's drug therapy</td>
<td>This patient received esomeprazole, a name-brand proton pump inhibitor. Generic omeprazole is now available and has similar efficacy. This patient received escitalopram, a name-selective serotonin reuptake inhibitor. Generic citalopram is now available and has similar efficacy.</td>
</tr>
<tr>
<td><strong>Drug available over the counter</strong></td>
<td>The receipt of a medication by prescription when it is available over-the-counter (OTC). Although many OTC medications are clinically useful and less costly alternatives to prescription drugs, we ask providers to use their judgment as to whether or not patients can purchase the item themselves.</td>
<td>This patient received docusate and diphenhydramine by prescription. These are available at a minimal cost OTC.</td>
</tr>
</tbody>
</table>
Prevalence of Drug-Related Problems and Cost-Savings Opportunities in Medicaid High Utilizers Identified by a Pharmacist-Run Drug Regimen Review Center

during the month that the patient exceeded the 7-medication limit. Data from prior months (up to a year) were used, if available and, if needed, to clarify concerns about utilization in the month of the review, such as duplicative therapy. Claims data from prior months would, of course, not be available to reviewers if the patient was not eligible for Medicaid benefits prior to the month of the review.

Nursing home (NH) and non-NH patients were reviewed, starting in May 2002. Each month, all patients who exceeded the 7-medication limit were ranked by the number of pharmacy claims submitted in that month. Top utilizers among NH and non-NH patients were reviewed if they had not been reviewed in the previous 6 months. The initial contract with the state called for DUR evaluation of 200 patients per month. Toward the end of the period of our analysis, in mid-2004, the contract was modified to expand the review number to 300 per month. Letters were generated and mailed to prescribers that addressed each specific drug-therapy concern. Some patients were reviewed a second time if they remained in the top 200 to 300 patients after 6 months.

Data from reviews conducted for patients who had exceeded the 7-medication limit in 2003-2004 were collated. If patients were reviewed multiple times during the 2-year period, data from subsequent reviews were excluded from analysis so that each patient was counted only once. The prevalence of clinically important DRPs and CSOs identified in each first review were calculated for NH and non-NH patients.

Results

A total of 391,890 Medicaid recipients were eligible for prescription benefits for at least 1 month during the calendar years 2003 and 2004. Of these, 242,411 (61.9%) had at least 1 pharmacy claim, and 16,958 (4.3%) exceeded the 7-medication limit. Among those exceeding the limit, we conducted a total of 4,563 reviews for 3,706 patients (21.9% of patients who exceeded the 7-medication limit), including 671 NH patients and 3,035 non-NH patients. A flowchart describing how patients were included for review is shown in Figure 1. Reviewed patients accounted for 1.5% of Medicaid eligible patients who filled prescriptions during the time period and 17.6% of total prescription drug costs during the time period. Demographics of reviewed patients are shown in Table 3. The mean age of reviewed patients was 53.5 years: 71.7 years for NH patients and 49.4 years for non-NH patients. Patients in both groups were predominantly female, including 71.2% of NH and 80.0% of non-NH patients.

Figure 2 shows the distribution of patients who had DRPs and CSOs. Of the reviewed patients, at least 1 DRP category was identified in 2,952 patients (79.7%), including 325 NH patients (48.4%) and 2,627 non-NH patients (86.6%). Multiple DRPs were identified in 2,080 patients (56.1%). Table 4 shows the numbers of patients who had each DRP category identified.

The most common categories identified included therapeutic duplications in 2,024 patients (54.6%), dose form optimization in 1,102 patients (29.7%), and inappropriate uncoordinated care in 939 patients (25.3%). The average pharmacy cost per month for patients with at least 1 DRP was $1,081. To put this number into perspective, the average pharmacy cost per month for all other patients receiving at least 1 prescription (including high- and low-utilizers) was $91.

Figure 3 shows the top 10 primary indications for drugs implicated in DRPs. The most common therapeutic category was pain and inflammation, which was implicated in 29.1% of all DRP categories identified. Other common categories included drugs used for anxiety or sleep (13.6%), antidepressants (11.6%), drugs for cardiovascular diseases (6.7%), drugs for psychotic disorders (6.4%), and cough and cold preparations (6.4%).
At least 1 CSO was also identified for 2,945 patients (79.5%), including 380 NH patients (56.6%) and 2,565 non-NH patients (84.5%). Table 5 shows the numbers of patients who had each CSO category identified. Multiple CSO categories were identified in 1,905 patients (51.4%). Reviewed patients with at least 1 CSO identified had an average drug cost of $1,109.60 during the review month. The most common CSO category identified was the recommendation to consider a therapeutic alternative to a prescribed drug, occurring in 2,695 reviews (72.7%).

CSOs=cost-savings opportunities; DRPs=drug-related problems.

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Discussion

At least 1 DRP or CSO was identified in 92% of all reviewed patients, including 76% of NH patients and 96% of ambulatory patients. The difference between NH and non-NH patients with respect to the prevalence of DRPs is not surprising when one considers the practice model for these patient groups. NH patients tend to have a single physician prescribing and a single pharmacy dispensing medications; they also have the benefit of a federally mandated monthly drug regimen review by a pharmacist, which would result in lower rates of problems associated with uncoordinated care. Not a single case of uncoordinated care was identified in our NH patients within the 2-year evaluation period. However, among non-NH patients, the largely fee-for-service reimbursement model in Utah creates an environment where ambulatory patients frequently receive care for the same disease state from multiple providers at different practice sites. It has been our observation that therapeutic duplications, our most common DRP category, are often associated with patients who receive care from multiple clinicians. In fact, 35% of our patients with a therapeutic duplication had an associated recommendation to coordinate care compared with only 13% of patients without therapeutic duplications (data not shown).

This finding suggests that some of the elements of the NH practice model could have a dramatic impact on the rate of DRPs in ambulatory patients if those elements could be applied to the ambulatory care setting. For example, the mandated monthly pharmacist reviews for NH patients, while a critical part of NH care, results in a disparity of care for non-NH patients. Greater pharmacist involvement in evaluating the drug regimens of non-NH patients may be warranted across the board. Similarly, these results provide a rationale for applying the single physician and pharmacy provider model to the ambulatory care setting, such as increasing enrollment in managed plans that require a gatekeeper provider. The state of Utah maintains a fee-for-service plan because it is not feasible to require patients in rural settings to join managed plans. This is due to concerns about potentially limiting access to health care providers. However, the fee-for-service model may, in fact, result in more DRPs, higher costs, and potentially greater harm to patients.

We made the recommendation to consider a drug therapy alternative in a high proportion (77%) of ambulatory patients. Breaking this number down, more than one third of these (34%) consisted of recommendations to switch from a name-brand prescription proton pump inhibitor to over-the-counter (OTC) omeprazole, also covered by Medicaid. We also recommended switching between statins to less expensive agents with similar efficacy in low-density lipoprotein cholesterol reduction (14%) and to switch from a prescription nonsedating antihistamine to loratadine OTC (8%), also covered by Medicaid.

The proportion of patients for whom a generic alternative was recommended was low in our analysis (3.7%). This is primarily because Utah’s DUR Board required mandatory switching of brand-name medications to generics midway through 2003. Fischer et al. evaluated this end point in 49 states in the year 2000 and found that an average of 6.1% of

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**TABLE 3** Demographics of Reviewed Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Female, Number (%)</th>
<th>Age Mean [SD]</th>
<th>Race: White, Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing home (N = 671)</td>
<td>478 (71.2)</td>
<td>71.7 [15.5]</td>
<td>645 (96.1)</td>
</tr>
<tr>
<td>Non-nursing home (N = 3,035)</td>
<td>2,428 (80.0)</td>
<td>49.4 [14.1]</td>
<td>2,917 (96.1)</td>
</tr>
<tr>
<td>Total (N = 3,706)</td>
<td>2,906 (78.4)</td>
<td>53.5 [16.7]</td>
<td>3,562 (96.1)</td>
</tr>
</tbody>
</table>

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**FIGURE 2** Percentages of Patients With DRPs and CSOs (N = 3,706)

- DRPs and CSOs (66%)
- No DRPs or CSOs (8%)
- CSOs Only (13%)
- DRPs Only (13%)

CSOs=cost-savings opportunities; DRPs=drug-related problems.
total drug expenditures (more than $228 million for all states) could have been saved in 2000 by using generics.

We were surprised to observe that 78% of our reviewed patients but only 55% of Medicaid enrollees in our state were female, suggesting that women are higher utilizers of prescription drugs. Other research has shown that women do, in fact, utilize health care resources more than men. While all of the reasons for this are unclear, theories include gender differences in the perception of illness and the likelihood of seeking treatment for illness, higher morbidity rates in women, and health differences associated with the reproductive system. In addition, the proportion of female NH patients might also be expected to be higher due to the differences in life expectancy between the genders.

Some of the DRP categories may be best assessed when ICD-9 codes from medical claims are available, including drug-disease interaction, treatment without an indication, and untreated indication. However, ICD-9 codes were not available for some patients, including those enrolled in managed Medicaid plans and any dual eligibles for whom a coinsurance claim was not submitted. In addition, when we made recommendations based on ICD-9 codes, we occasionally received feedback from clinicians indicating that some of the ICD-9 codes were incorrect and that, in fact, some patients did not have a diagnosis that was indicated on a medical claim. Thus, we also used information from prescription claims as a surrogate for diagnosis where it was possible to do so. For example, if a patient received blood glucose testing supplies on a monthly basis, we felt

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**TABLE 4** Frequency and Prevalence of Drug-Related Problems Considered Clinically Important

<table>
<thead>
<tr>
<th>Drug-Related Problem Category</th>
<th>Patients With at Least 1 DRP (%)</th>
<th>Patients With 2 or More DRPs (%)</th>
<th>Patients With at Least 1 DRP (%)</th>
<th>Patients With 2 or More DRPs (%)</th>
<th>Patients With at Least 1 DRP (%)</th>
<th>Patients With 2 or More DRPs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic duplication</td>
<td>140 (20.9)</td>
<td>23 (3.4)</td>
<td>1,884 (62.1)</td>
<td>800 (26.4)</td>
<td>2,024 (54.6)</td>
<td>823 (22.2)</td>
</tr>
<tr>
<td>Dose form not optimized</td>
<td>171 (25.5)</td>
<td>29 (4.3)</td>
<td>931 (30.7)</td>
<td>234 (7.7)</td>
<td>1,102 (29.7)</td>
<td>263 (7.1)</td>
</tr>
<tr>
<td>Coordinate care</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>939 (30.9)</td>
<td>344 (11.3)</td>
<td>939 (25.3)</td>
<td>344 (9.3)</td>
</tr>
<tr>
<td>Untreated indication</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>298 (9.8)</td>
<td>49 (1.6)</td>
<td>298 (8.0)</td>
<td>49 (1.3)</td>
</tr>
<tr>
<td>Duration exceeds usual</td>
<td>15 (2.2)</td>
<td>0 (0.0)</td>
<td>279 (9.2)</td>
<td>12 (0.4)</td>
<td>294 (7.9)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>9 (1.3)</td>
<td>1 (0.1)</td>
<td>284 (9.4)</td>
<td>38 (1.3)</td>
<td>293 (7.9)</td>
<td>39 (1.1)</td>
</tr>
<tr>
<td>Additive toxicity</td>
<td>2 (0.3)</td>
<td>0 (0.0)</td>
<td>207 (6.8)</td>
<td>12 (0.4)</td>
<td>209 (5.6)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>Drug-disease interactions</td>
<td>25 (3.7)</td>
<td>0 (0.0)</td>
<td>181 (6.0)</td>
<td>26 (0.9)</td>
<td>206 (5.6)</td>
<td>26 (0.7)</td>
</tr>
<tr>
<td>Dose exceeds usual</td>
<td>32 (4.8)</td>
<td>2 (0.3)</td>
<td>143 (4.7)</td>
<td>7 (0.2)</td>
<td>175 (4.7)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment without an</td>
<td>32 (4.8)</td>
<td>1 (0.1)</td>
<td>77 (2.5)</td>
<td>0 (0.0)</td>
<td>109 (2.9)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtherapeutic dose</td>
<td>2 (0.3)</td>
<td>0 (0.0)</td>
<td>62 (2.0)</td>
<td>2 (0.1)</td>
<td>64 (1.7)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Any DRP category*</td>
<td>325 (48.4)</td>
<td>122 (18.2)</td>
<td>2,627 (86.6)</td>
<td>1,958 (64.5)</td>
<td>2,952 (79.7)</td>
<td>2,080 (56.1)</td>
</tr>
</tbody>
</table>

* Prevalence of DRP recommendations, regardless of DRP type.

DRP=drug-related problem; NH=nursing home patients.

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**FIGURE 3** Incidence of Top 10 Primary Indications for Drugs Implicated in DRPs

- Pain or Inflammation (29.1%)
- Anxiety or Sleep (13.6%)
- Depression (11.6%)
- Cardiovascular Diseases (6.7%)
- Psychotic Disorders (6.4%)
- Cough, Cold, or Allergy (6.4%)
- Asthma or COPD (5.0%)
- Other GI Disorders (4.8%)
- Infectious Diseases (4.0%)
- Seizure Disorders (2.5%)

COPD=chronic obstructive pulmonary disease; DRP=drug-related problem; GI=gastrointestinal.
The recommendation
whereas Drug Regimen Review Center (DRRC)
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or assessing the appropriateness of

Prevalence of CSO recommendations, regardless of CSO type. CSO= cost-savings opportunity; NH= nursing home patients; OTC= over the counter.

<table>
<thead>
<tr>
<th>Drug-Related Problem Category</th>
<th>NH (N = 671)</th>
<th>Non-NH (N = 3,035)</th>
<th>Total (N = 3,706)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients With</td>
<td>Patients With</td>
<td>Patients With</td>
</tr>
<tr>
<td></td>
<td>at Least 1</td>
<td>2 or More</td>
<td>at Least 1</td>
</tr>
<tr>
<td>Brand name dispensed</td>
<td>3 (0.4)</td>
<td>0 (0.0)</td>
<td>135 (4.4)</td>
</tr>
<tr>
<td>Consider therapeutic alternatives</td>
<td>357 (53.2)</td>
<td>84 (12.5)</td>
<td>2,338 (77.0)</td>
</tr>
<tr>
<td>Drug available OTC</td>
<td>46 (6.9)</td>
<td>2 (0.3)</td>
<td>1,081 (35.6)</td>
</tr>
<tr>
<td>Any CSO category*</td>
<td>380 (56.6)</td>
<td>106 (15.8)</td>
<td>2,565 (84.5)</td>
</tr>
</tbody>
</table>

*Prevalence of CSO recommendations, regardless of CSO type. CSO=cost-savings opportunity; NH=nursing home patients; OTC=over the counter.

comfortable assuming the patient had diabetes, regardless of whether the patient had a diagnosis code in medical or facility claims. However, it should be noted that the limited information we had for some patients may have resulted in an underestimate of the true prevalence of these DRP categories in our patient sample.

The recommendation to optimize a dosage form included 2 separate types of recommendations: (1) to decrease the total number of tablets or capsules for certain medications or (2) to switch to a combination product from 2 separate dosage forms. In the first case, for example, a patient who received a total of 60 olanzapine 5 mg tablets as a 30-day supply would trigger the suggestion to use 10 mg olanzapine tablets since it is usually dosed once daily. Another scenario might be to suggest tablets-splitting, if appropriate. For example, if a patient was receiving sertraline 50 mg daily, use of the 100 mg tablets might be suggested since these tablets are scored and have nearly an identical cost per tablet. These types of dose form optimization strategies have been successfully implemented in other Medicaid programs.18

In the second case, the use of combination products is recommended when it would save costs, which is not always the case. For example, based on reimbursement amounts, the combination of simvastatin/ezetimibe was less costly than the 2 dosage forms used separately during the period of analysis, so the use of the combination product was recommended if patients were already taking both agents separately. However, we did not make the recommendation to switch to a combination product if the combination product was more expensive than the 2 dosage forms separately, such as with diclofenac/misoprostol. We did not consider OBRA-mandated rebate amounts in our assessment of the costs of drug therapy for 2 reasons: (1) we did not have ready access to the rebate amounts by drug and (2) although we could have pursued the reporting of rebate amounts for our program, we did not want to create a situation where our recommendations might change periodically, as often as quarterly, based on rebate amounts. Therefore, the recommendations for therapy selection were independent of rebate amounts that were required by statute and varied somewhat during the 2-year period of this intervention.

Our recommendation to have the patient purchase a drug out-of-pocket if it was available OTC was less frequently used after initial implementation of our program. Although we reported a relatively high prevalence (30% of reviewed patients), for this DRP, this recommendation was discontinued midway through 2003. In part, the recommendation was discontinued due to concerns about restricting the use of effective and beneficial OTC agents, which may result in increased costs and decreased health among Medicaid patients.19 The recommendation was used initially because there was genuine concern that the 7-medication limit was going to be implemented at the pharmacy level after a period of review, so a goal of our program was to help patients identify the best way to cut their number of prescriptions down to 7. The spirit of the recommendation was to help identify the least expensive agents for patients to purchase out-of-pocket, if needed. However, as it became clear that most high utilizers were very ill patients with multiple disease states, many of whom required at least 7 medications for appropriate management, concerns that the 7-medication limit would be implemented soon dissipated, and we discontinued use of this recommendation.

To the best of our knowledge, our program is unique in that pharmacists identify specific DRP categories in patients rather than the alternative approach of applying programmed algorithms to large datasets and producing generic interventions for large numbers of patients. Based on our anecdotal experience reviewing thousands of patients on a case-by-case basis, patients are unique in attributes related to medical history and comorbidities. Frequently, recommendations that we make in one patient do not apply to another. Thus, it is difficult to make direct comparisons to other studies. Additionally, other interventions have frequently addressed only single specific recommendations or DRPs, such as identifying inappropriate usage of drugs in the elderly9,10 or assessing the appropriateness of HIV treatment,4 whereas Drug Regimen Review Center (DRRC) reviewers in the present study attempted to address each patient’s entire history of diseases and drug utilization.
Limitations

Some critics may cite the lack of a standardized, evidence-based protocol for defining DRPs and CSOs as a principal limitation of the analysis. DRP and CSO categories were defined by consensus among a group of 5 pharmacists with varying clinical backgrounds prior to implementation of the DRRC. The categories were created for the sole purpose of quantifying the types of problems that we identified and to assist us in making recommendations to clinicians. Individual patients have diverse and specific issues related to their drug therapy that are difficult to capture using a few broad categories. Our specific recommendations within each category were tailored for each patient using evidence-based guidelines where they exist for the different therapeutic areas. For example, we use the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) as a basis to recommend that patients with hypertension receive a low-dose thiazide diuretic as a first-line agent for blood-pressure lowering. We also use evidence-based guidelines for recommendations in other disease states, including diabetes, asthma, heart failure, and treatment of symptoms of menopause.

Another limitation is that we did not systematically evaluate the impact of our program on costs or outcomes in this descriptive analysis. Since the goal of our program is to ensure appropriate pharmacotherapy among as many Medicaid patients as possible, we conducted reviews systematically on patients who exceeded the threshold of 7 medications per month. Consequently, we do not have a control group similar in demographics and comorbidities for comparison, and we have not employed an experimental design to permit the evaluation of outcomes. However, we have tracked pharmacy costs for reviewed patients over time in an effort to quantify what happened with drug costs for reviewed patients in the months following a review. These trends are reported in our annual report, which is available online. We made 3 estimates from the most conservative (drug costs in the reviewed cohorts would have remained constant for the year following the review) to the most probable (drug costs in the reviewed cohorts would have increased at a rate of 15%, similar to the rate of increase seen across all Medicaid patients). Using these 3 scenarios, we projected 1-year savings ranging from $4.6 to $8.1 million in our reviewed patients alone.

Another limitation is that the identification of DRPs is subjective and is based on the clinical experience and judgment of our reviewers. Thus, a similar program conducted by a different group of pharmacists might result in different prevalence rates of DRPs. While we feel confident that our method of identifying DRPs is clinically sound, in that we can incorporate into our consideration a number of variables that automated programs may not be able to evaluate, we have implemented strategies aimed at reducing variability between pharmacists in these assessments. A future research goal is to evaluate pharmacist uniformity in recommendation categories and rates before and after implementation of these quality-assurance efforts.

An additional limitation to the external generalizable ability of our analysis is that the rates of DRPs and CSOs are largely dependent on the policies of the Utah Medicaid program. For example, states that do not mandate use of generics are likely to find a higher rate of brand-name use. Other policies that might impact the rates of problems identified include prior-authorization requirements, preferred drug lists, fail-first requirements, class restrictions, and quantity limitations. The state of Utah uses several cost-saving measures, including patient copays for the first 5 prescriptions; fail-first and prior-authorization requirements for certain classes (e.g., nonsedating antihistamines); quantity limits for several therapeutic classes, including proton pump inhibitors and benzodiazepines; and no reimbursement for drug efficacy study implementation (DESI)-class drugs considered to have marginal benefit. The state of Utah has considered but has not yet implemented a preferred-drug list.

Finally, a limitation of all evaluations of pharmacy claims data is the lack of information about the use of physician office samples in patients. This limitation might lead us to identify a higher rate of untreated indications if many patients were receiving samples instead of filling prescriptions in the pharmacy. We think it is unlikely that many Medicaid patients receive samples on a long-term basis since patients have a minimal or no copay for medications covered by Medicaid, and our Medicaid program generously pays for most drugs with few restrictions. However, we have no data to support the assumption that physicians do not frequently give samples to patients in the Utah Medicaid program.

One area for future research in our program is to try to determine whether there is a difference in DRPs and CSOs among fee-for-service versus managed care plans. Because Utah is considered a frontier state, based on population density, it is not feasible to require all Medicaid recipients to enroll in managed care plans. Consequently the state of Utah has many Medicaid recipients in managed care and fee-for-service plan types. Our center reviews patients from both plan types, but we have not compared DRP and CSO prevalence rates between managed Medicaid and fee-for-service care. Since we have observed a high correlation between therapeutic duplications and uncoordinated care, it might be interesting to determine if patients in managed care plans have better coordinated care and fewer DRPs. The current study did not assess this relationship.

Conclusions

One or more drug-related problems occurred in 48% of nursing home residents who received 7 or more medications per month and in 87% of nonresidents of nursing homes, for an overall prevalence of 80% of high-utilizing Medicaid recipients. Therapeutic duplication was the most common problem identified among Medicaid recipients. At least 1 CSO was found...
for 57% of the nursing home residents and 85% of the ambulatory recipients, yielding an overall prevalence of 80% of high-utilizing Medicaid recipients; 54.1% of patients had 2 or more CSOs. Future research is needed to determine if managed care plans have lower rates of drug-related problems compared with fee-for-service plans.

DISCLOSURES

Funding for this study was provided by the Utah Department of Health and was obtained by author Gary M. Oderda. A portion of these data were presented as a poster at the American College of Clinical Pharmacy Updates in Therapeutics: The Pharmacotherapy Preparatory Course and Spring Practice and Research Forum in Myrtle Beach, SC, April 2005. Author Joanne LaFleur served as principal author of the study. Study concept and design were contributed by G. Oderda, with input from LaFleur. Data collection was the work of LaFleur and authors Carrie Ann McBeth, Lynda Oderda, and Carin Steinvoort; data interpretation was the work of LaFleur, McBeth, G. Oderda, and author Karen Gunning. Writing of the manuscript was the work of LaFleur and McBeth; its revisions were the work of all authors. The authors disclose no potential bias or conflict of interest relating to this article.

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False-Positive Versus True-Positive Drug-Drug Interactions With Warfarin

Warfarin is a marvelous, life-saving drug in the prevention of atherothrombotic events such as myocardial infarction, stroke, venous thromboembolism, and, indeed, vein thrombosis. However, warfarin has somewhat unpredictable anticoagulant effects that require continuous monitoring of prothrombin time and the international normalization ratio (INR), and the search continues for a drug with efficacy comparable to warfarin but with lower risk of over- and underanticoagulation.1

The need for continuous monitoring of warfarin is magnified by the potential for drug-drug interactions. Today, there are 225 drug-drug interactions listed in Facts and Comparisons for warfarin, of which 79 are categorized as a Level 1 interaction, the highest severity level.2 A Level 1 interaction is described as: “Potentially severe or life-threatening interaction; occurrence has been suspected, established or probable in well-controlled studies. Contraindicated drug combinations may also have this number.” Another 48 drugs are listed as Level 2 interaction, “Interaction may cause deterioration in a patient’s clinical status; occurrence suspected, established or probable in well controlled studies.”

Curiously, in this issue of JMCP, Zhang et al. in their examination of medical and pharmacy administrative claims found that only metronidazole and the cephalosporins in concomitant use with warfarin were associated with bleeding events as recorded on medical claims.3 On its face, this finding might suggest that patient safety could be improved by electronic prescribing via a decision support tool to detect these drug-drug interactions prior to dispensing. Metronidazole is listed as a Level 1 drug-drug interaction in the Facts and Comparisons interaction database, and the cephalosporins that are listed in the drug-drug interaction database (cefazolin, cefotetan, cefoxitin, and ceftriaxone) are Level 2 interactions. However all 4 cephalosporins are injectable, not oral dose forms, and the research performed by Zhang et al. did not include injectable cephalosporins. In other words, in the research performed by Zhang et al. of administrative claim records for the drugs associated with bleeding events when used with warfarin, only 1 drug, metronidazole, is listed in a commonly used drug-drug interaction database. Therefore, electronic surveillance of concomitant drug use would not have detected the apparent interaction with oral cephalosporins unless the drug-drug interaction filter was set at the class level and not the drug-specific level.

In addition to the possible false-positive interaction of warfarin with oral cephalosporins, the research performed by Zhang et al. is equally important for what it did not find. Specific Level 1 interactions with nonsteroidal anti-inflammatory drugs (NSAIDs), barbiturates, cimetidine, ciprofloxacin, amiodarone, and Level 2 interactions with carbamazepine, chloramphenicol, griseofulvin, and rifampin were not associated with bleeding events as recorded in medical claims. In other words, these Level 1 and Level 2 interactions would generate potentially false-positive warnings in an electronic decision support system for prescribing.

There is another point worth noting in the research performed by Zhang et al. Of the drugs selected by the researchers for study, imipramine, co-trimoxazole, and carbencilin are not listed in any of the 4 severity levels among the drug-drug interactions with warfarin in the current version of Facts and Comparisons Drug Interaction Facts. Although not mentioned by the authors in the results or discussion of their findings, these 3 drugs were presumably used to confirm the true negative interaction with warfarin.

So, the tally in the research reported by Zhang et al. is 1 true-positive interaction out of 225 potential drug-drug interactions and 3 apparent true-negative interactions. Based on these research findings, a decision-support tool in an electronic prescribing system would generate false-positive messages for interactions with dozens of drugs such as the NSAIDs, and false-negative interactions of warfarin with the oral cephalosporins would occur. On the other hand, research such as this, with administrative claims data, cannot inform us about the key coincidental events. It is entirely possible that the drug interaction occurred without clinical consequence because the dose of warfarin was changed, perhaps by a clinical pharmacist working in collaboration with a physician.

The present study by Zhang et al. does remind us of the many areas of research yet to pursue. Administrative claims data in the United States will not permit us, in most cases, to adequately study the relationship of nonprescription drug use, such as aspirin, acetaminophen, or over-the-counter NSAIDs such as ibuprofen, on outcomes such as bleeding events. Administrative claims data in the United States will also not support assessment of the hypothesis that alcohol consumption, for example, may contribute to an increased risk of bleeding for the Level 2 drug-drug interaction of warfarin with statin drugs such as lovastatin. For this hypothesis, a randomized, controlled trial is necessary to determine that the risks of an international normalized ratio (INR) of 2.0 or higher are not different among men categorized as nondrinkers, light, moderate, or heavier drinkers.4

On the other hand, administrative claims data may help assess the incidence and prevalence of bleeding episodes associated with use of single and combined antithrombotic drug therapy. Warfarin, for example, is used increasingly with antiplatelet drugs such as dipyridamole or clopidogrel, particularly in patients with multiple indications such as coincident atrial fibrillation and ischemic heart disease. Hallas et al. reported this month in BMJ the results of research with comprehensive administrative data from Denmark in which the risk of upper gastrointestinal (GI) bleeding was 1.1 (95% confidence interval [CI], 0.6-2.1) for clopidogrel, 1.8 (95% CI, 1.5-2.1) for low-dose aspirin, 1.9 (95% CI, 1.3-2.8) for dipyridamole, and 1.8...
(1.3-2.4) for vitamin K antagonists (such as warfarin). Combined use of these drugs significantly increased the risk of GI bleeding, to 2.3 (1.7-3.3) for dipyridamole with aspirin, 5.3 (2.9-9.5) for vitamin K antagonists with aspirin, and 7.4 (3.5-15) for clopidogrel with aspirin. During the study period, from 2000 through 2004, exposure to combined antithrombotic regimens increased by 425% in the population of 470,000 residents of Funen County, Denmark.

Some prominent medical journals have banned, for some time, the use of conclusions in articles that “more research is needed” on this subject. However, the findings in the article by Zhang et al. beg for more research.

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Rhythm Versus Safety in Amiodarone Therapy

Amiodarone (Cordarone, Pacerone) is a powerful antiarrhythmic that is effective in converting atrial fibrillation (AF) to sinus rhythm and superior to sotalol in maintaining sinus rhythm. In 665 patients who were receiving anticoagulants and had persistent AF, Singh et al. found a median time to recurrence of AF of 487 days in the amiodarone group versus 74 days in the sotalol group and 6 days in the placebo group, with improved quality of life and improved exercise performance in the amiodarone group. In this study known as the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), spontaneous conversion occurred in 72.1% of amiodarone patients, 24.2% for sotalol, and 0.8% for placebo. However, the use of amiodarone in AF is not approved by the U.S. Food and Drug Administration (FDA). The unlabeled (off-label) uses of amiodarone include conversion of atrial fibrillation and maintenance of sinus rhythm, and treatment of supraventricular tachycardia.

Amiodarone has also been shown to be a useful antiarrhythmic in patients after cardiac surgery in the clinical trial known as PAPABEAR (Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) in which atrial tachyarrhythmia occurred less frequently in amiodarone patients (16.2%) compared with placebo (29.5%). The overall hazard ratio (HR) for tachyarrhythmia was 0.52 (95% confidence interval [CI], 0.34-0.69), and the HR was significantly less than 1.0 for all subgroups of patients, including patients younger than 65 years, patients aged 65 years or older, patients who had coronary artery bypass graft (CABG) only, patients who had valve replacement/repair surgery with or without CABG surgery, patients who received preoperative beta-blocker therapy, and patients who did not receive preoperative beta-blocker therapy.

Assessment of the medical treatment of AF from 1991 to 2000 showed that amiodarone replaced quinidine as the dominant sinus rhythm drug by 2000. For 1,355 visits for patients with AF obtained from the National Ambulatory Medical Care Survey (NAMCS), a nationally representative assessment of office-based physician practice, overall use of drugs to control cardiac rhythm decreased from 72% of visits in 1991-1992 to 56% in 1999-2000 (P = 0.01 for trend) due to declining digoxin use (64% to 37%, P <0.001 for trend). The absolute rate of use of beta-blockers, calcium channel blockers, and sinus rhythm medication did not change over the 10 years, but amiodarone use increased from 0.2% to 6.4% (P <0.001 for trend) while quinidine use decreased from 5.0% to 0.0% (P =0.01 for trend).

The direct cost of amiodarone is not a factor in its use today. Amiodarone was approved by the FDA on December 27, 1985, as the product Cordinaro. Since it was approved more than 20 years ago, it has been available by generic name for several years. The average managed care organization price per day of therapy in 2006 is $2.00 or less.
While amiodarone is relatively cheap, it is associated with significant toxicity. In a prospective study of 403 patients with AF, Roy et al. found amiodarone reduced the recurrence of AF to 35\% versus 63\% for sotalol, but adverse events contributed to discontinuation of drug therapy in 18\% of patients receiving amiodarone versus 11\% of those treated with sotalol or propafenone.\(^6\) In the 2006 Guidelines for the Management of Patients with Atrial Fibrillation from the American College of Cardiology, American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology, amiodarone is positioned as alternate second-line therapy to digoxin in AF patients with heart failure, but warnings include pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia.\(^7\) Amiodarone also is classified as a Level 1 risk to cause torsades de pointes, although the likelihood is listed as “low.”\(^8\)

Package labeling for amiodarone lists a host of potential toxicities, several of which may be fatal. The most important toxicity in amiodarone package labeling is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis), which occurs in as many as 10\% to 17\% of patients with ventricular arrhythmias at doses of about 400 mg/day, but the reported prevalence of pulmonary toxicity is 2\% to 7\% in most clinical trials of amiodarone.\(^2\) However, pulmonary toxicity secondary to amiodarone is fatal in about 10\% of the cases.

Compared with pulmonary toxicity, liver injury is “common” with amiodarone, evidenced by elevated liver enzymes, but is usually mild and asymptomatic. Guidelines for the use and monitoring of amiodarone from the American Academy of Family Physicians list a prevalence of 1\% for liver toxicity associated with amiodarone as measured by liver enzyme levels 3 times higher than normal.\(^9\) However, overt liver disease can occur with amiodarone and, while rare, can be fatal.\(^10\) Hypothyroidism occurs in 2\% to 10\% of patients who receive amiodarone, and hyperthyroidism occurs in about 2\% of patients.

Other concerns include the possible development of significant heart block or sinus bradycardia in 2\% to 5\% of patients who receive amiodarone and possible exacerbation of arrhythmia that may make the arrhythmia less well tolerated and more difficult to reverse, also in 2\% to 5\% of patients. Therefore, the package label for amiodarone suggests the use of amiodarone as second-line therapy in ventricular arrhythmias, consistent with second-line status for amiodarone in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation.

In May 2005, amiodarone was the subject of a Dear Healthcare Professional letter from the FDA warning of potentially fatal pulmonary toxicity, hepatic injury and worsened arrhythmia.\(^11\) The product label in 2006 includes a “black box” warning that amiodarone should be used only in patients with life-threatening ventricular arrhythmias due to substantial toxicity associated with its use. For patient safety, the product label for amiodarone recommends monitoring of liver enzymes on a “regular basis” without specific recommendations on what constitutes a “regular basis.” Thyroid function monitoring is recommended at “baseline and periodically during therapy”; “periodically” is not defined.

Raebel et al. in this issue of JMCP take a tight window of 6 months follow-up to proclaim that amiodarone patients in 10 HMOs were shortchanged in liver and thyroid function monitoring during a data capture period in 1999-2001.\(^12\) While the toxicities associated with the use of amiodarone have been known for some time, its use increased significantly by 1999-2000, particularly in AF patients. Certainly, the risks associated with amiodarone are more prominent today than in 1999-2001. So, judgment of clinician adherence to monitoring guidelines and protection of patient safety needs to be tempered with observation of the time period examined.

There may also be a methodological concern in the study by Raebel et al. that would suggest that the clinicians who cared for the patients in the 10 HMOs may not be guilty of under-care. In addition to the fact that the product label for amiodarone is not specific with respect to what constitutes either “regular” or “periodic” monitoring, it is possible that many patients were loaded with amiodarone as inpatients, as recommended in dose administration instructions in the product label. A total of 39\% of patients in this study had 1 or more hospitalizations in the 6-month period prior to an outpatient claim for amiodarone, and 22\% were hospitalized 1 or more times during the average 6-month period following the first outpatient claim for amiodarone. Since Raebel et al. did not have consistent records of inpatient laboratory tests, their reported rate of laboratory monitoring for liver function and thyroid function may be understated. Both liver function, measured by alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and thyroid function, measured by thyroid-stimulating hormone (TSH), are components of general laboratory panels.

The authors did, however, assess the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the medical claims relative to the medical record. While medical claims generally did a good to excellent job of representing the medical record, the NPV of 73\% for thyroid function tests indicates that 27\% of the negatives (i.e., a finding that no laboratory testing took place according to the medical claims data) were actually false-negative (i.e., testing did occur according to documentation in the medical record).

The methodology employed in the study by Raebel et al. is also associated with possible overestimation of the average exposure to amiodarone. The data reported in Table 4 of that article show that 19\% of patients received 2 “dispensings” or less, and 45\% of patients received 3 dispensings or less of amiodarone in the average 6-month follow-up period. Since a mail-service pharmacy option with a days supply greater than 1 month was uncommon in the 10 HMOs at the time and...
pharmacy benefits generally restricted each dispensing to a 1-month supply, it appears possible that some of the amiodarone patients did not receive amiodarone during the entire 6-month follow-up. Since the researchers did not collect days supply as part of their study design, the median and range of actual days supply of amiodarone dispensed to these patients are unknown. Discontinuation of amiodarone therapy would be cause for discontinuation of laboratory monitoring for side effects of amiodarone.

Also left unanswered in the study by Raebel et al. are questions about the safety of amiodarone in combination with other drugs. Amiodarone is metabolized by the cytochrome P450 enzyme, resulting in many potential drug-drug interactions. About 18 months after the close of the data collection period in the study by Raebel et al., the label for simvastatin (Zocor) was changed in June 2002 to include a warning specific for coincident use with amiodarone. The label change was approved by the FDA on May 6, 2002, making simvastatin the only statin available in the United States with drug interaction warning specific to amiodarone.

Monitoring patient response to therapy and threats to patient safety are important quality initiatives now and in the future. A study of the quality of amiodarone monitoring performed today would presumably include laboratory monitoring for pulmonary function, capture and reporting the number of days supply of amiodarone dispensed (to more accurately estimate actual drug exposure), the dose of amiodarone dispensed per day (to more accurately estimate dose titration as well as the quantity of drug exposed to the patient), the specific indication for use of the drug in each patient, and concomitant use with drugs that are contraindicated or that otherwise have warnings regarding coincident use. Even expert practitioners can miss the drug interaction between amiodarone and simvastatin, as evidenced in an April 2003 case report involving rhabdomyolysis in a 77-year old male evaluated nearly 1 year after the addition of the specific warning to the label of simvastatin for its interaction with amiodarone. And, assessment of the adequacy of monitoring therapy with amiodarone to protect patient safety would continue for longer than 6 months, particularly since amiodarone is a drug used in high-risk patients in whom toxicity as manifest by either liver enzymes or TSH levels is quite likely secondary to patient survival, particularly in a period as short as 6 months.

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5. Data search performed October 6, 2006, of the data warehouse of a national pharmacy benefits manager representing approximately 500,000 beneficiaries of small employer drug benefit plans for pharmacy claims with dates of service from July 1, 2006, through September 30, 2006.
What Evidence Supports Guidelines for Use of ACE Inhibitors and ARBs in Diabetes?

In this issue of JMCP, Cooke and Fatodu inform us that of 1,698 patients with diabetes, 13% (n=215) had a medical claim indicating renal involvement. In the subset of 215 diabetes patients with renal involvement, 177 had at least 1 medical claim with a diagnosis of hypertension, and the use of angiotensin-converting enzyme (ACEs) inhibitors or angiotensin receptor blockers (ARBs) was high (85.3%, n = 151). In the subgroup of 38 diabetes patients with renal involvement but without hypertension, the use of ACE inhibitors or ARBs was significantly lower (47%, n = 18, P <0.001). Overall, these administrative claims data for the dates of service from April 1, 2001, through March 31, 2002, revealed that 915 (53.9%) of the diabetes patients had at least 1 claim for either an ACE inhibitor or ARB. Relying on the 2002 and 2004 position statements of the American Diabetes Association on hypertension management in adults with diabetes, Cooke and Fatodu suggest that diabetes patients are undertreated with ACE inhibitors or ARBs. However, for their subgroup of patients with diabetes and hypertension (n = 1,072, 63.1%), more than 4 out of 5 (n = 951, 85.4%) were treated with an ACE inhibitor or ARB, and the authors acknowledge that only 20 diabetes patients (1.2% overall) who did not have hypertension but did have evidence of renal involvement did not receive either an ACE inhibitor or ARB.

While Cooke and Fatodu have support from clinical practice guidelines to claim undertreatment of diabetes patients with ACE inhibitors or ARBs, some scientists have recently questioned the evidence to support these guidelines. The results of a systematic review and meta-analysis performed last year for studies published through January 2005 refute the assumption that ACE inhibitors and ARBs, collectively renin-angiotensin system (RAS) inhibitors, have renoprotective effects that extend beyond reduction in blood pressure. Casas et al. concluded that not only are the additional renoprotective actions of ACE inhibitors and ARBs beyond lowering blood pressure unproven in persons with diabetes, there is not sufficient evidence to conclude that there is renoprotection from these drugs in nondiabetic patients with renal disease.

Specifically, Casas et al. found a relative risk of 0.71 for doubling of serum creatinine for the RAS inhibitors, but the 95% confidence interval (CI, 0.49-1.04) crossed 1.0 (i.e., no risk reduction), and a small benefit on end-stage renal disease (ESRD, relative risk, 0.87; 95% CI, 0.75-0.99). When Casas et al. analyzed the results by study population size, there was a smaller benefit in large studies. For patients with diabetic nephropathy, there was no benefit for RAS inhibitors by the measure of a 2-fold increase in serum creatinine (relative risk, 1.09; 95% CI, 0.55-2.15) and no benefit in progression to ESRD (relative risk, 0.89; 95% CI, 0.74-1.07), glomerular filtration rate, or absolute creatinine amounts. This systematic review and meta-analysis of data from 13 studies generated a firestorm response, generally focused on the heavy reliance on the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Casas and coauthors pointed out in rebuttal to the letters that the ALLHAT results did contribute about half of the available evidence on renal outcomes, but ALLHAT included renal disease as a prespecified outcome, and ALLHAT is the only study with a population size near the size necessary (57,000) to demonstrate a 10% relative risk reduction in ESRD.

Aside from the specific question regarding the potential value of ACE inhibitors or ARBs in renoprotection beyond blood pressure reduction, the results of key clinical trials suggested that there might be some effect of ACE inhibitors on glucose metabolism and a potential role in diabetes prevention. Two studies in particular, neither of which was designed to assess specifically the outcome of a new diagnosis of diabetes, suggested that ACE inhibitors might be associated with a side effect in preventing diabetes. Ingelﬁnger and Solomon in an editorial published earlier this month inform us that the Captopril Prevention Project (CAPPP) found a 14% lower incidence of diabetes in the captopril group compared with diuretics or beta-blockers in hypertensive patients, and results of the Heart Outcomes Prevention Evaluation (HOPE) Study in patients at high risk for cardiovascular events found a 34% reduction in risk of newly diagnosed diabetes in patients who received ramipril 10 mg per day compared with placebo. However, the absolute rates of a new diagnosis of diabetes were small. For the 5 years of follow-up in the HOPE Study, 102 (3.6%) patients in the ramipril arm developed a new diagnosis for diabetes versus 155 (5.4%) for placebo. In a study designed specifically to assess the development of a new diagnosis of diabetes in patients with either impaired glucose tolerance or impaired fasting glucose levels, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) results showed no difference in new diagnosis of diabetes for an average 3 years of therapy with ramipril (up to 15 mg per day), 17.1% versus 18.5% for placebo, (hazard ratio [HR], 0.91; 95% CI, 0.80-1.03).

The choice of a preferred antihypertensive agent in a particular patient involves consideration of multiple factors. ALLHAT results showed that compared with the diuretic chlorthalidone, the ACE inhibitor lisinopril was associated with a higher risk of stroke (P = 0.02) and a higher risk of cardiovascular disease (P <0.001), including a higher risk of heart failure and higher risk of coronary revascularization. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial involving 15,245 patients at high risk for cardiac events, including 31.7% with diabetes, found no difference in the primary composite outcome of sudden cardiac death, fatal myocardial infarction (MI), cardiovascular death, or cardiovascular morbidity (including heart failure) between the ARB valsartan and amlopidine. However, valsartan had a smaller effect compared with amlo-
dipine on blood-pressure lowering and had an increased risk of MI (HR, 1.19; P <0.02).13

Two major trials have compared ACE inhibitors to ARBs in cardiovascular outcomes. The Evaluation of Losartan In The Elderly (ELITE) II trial showed that the ARB losartan was not superior to the ACE inhibitor captopril in reducing morbidity and mortality in patients with heart failure, and the HR for sudden death was close to significant (HR, 1.30; 95% CI, 1.00-1.69) for losartan versus captopril.13 The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) also failed to show an advantage for ARBs over ACE inhibitors; in fact, most end points showed a trend in favor of captopril over losartan, with cardiovascular death significantly lower in the captopril group.14

Until more evidence accumulates on the alleged renoprotection associated with RAS inhibition, it seems reasonable for clinicians to not use pharmacologic intervention with ACE inhibitors or ARBs in normotensive patients with diabetes. For hypertensive patients with diabetes, prescribing a thiazide diuretic would also seem to represent the practice of evidence-based medicine. On the other hand, a combination product containing hydrochlorothiazide (HCTZ) and an ACE inhibitor such as benazepril or lisinopril has a managed care price before member cost share of about $0.70 per day or $21 per month compared with about $0.50 per day or $15 per month with either benazepril or lisinopril alone.15 While we await evidence of a renoprotective effect of RAS inhibition, the combination product of HCTZ and an ACE inhibitor appears to be a good investment to produce desired clinical outcomes in hypertensive patients with diabetes.

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15. Data search performed October 6, 2006, of the data warehouse of a national pharmacy beneﬁts manager representing approximately 500,000 beneﬁciaries of small employer drug benefit plans for pharmacy claims with dates of service from July 1, 2006, through September 30, 2006.
Prevalence of Phosphodiesterase-5 Inhibitor Use in the VHA in 2004 and 2005 Is Twice That of a Commercial Health Plan in 2001

To the Editor:

Cooke et al. in a previous issue of JMCP reported prevalence of phosphodiesterase-5 inhibitor (PDE-5) use of 54.1 per 1,000 male members aged 18 years or older (mean age: 53.1 years, SD: 10.4, median: 53 years) in a 1.2 million-member managed care organization located in the mid-Atlantic states. Sildenafil (Viagra) was the only PDE-5 drug on the market at the time, since vardenafil (Levitra) was approved by the U.S. Food and Drug Administration on August 19, 2003, and tadalafil (Cialis) on November 21, 2003. We were curious to determine how this prevalence of PDE-5 use compares with the Veterans Health Administration (VHA) system.

The VHA is a horizontally and vertically integrated health care system that served more than 5.2 million male patients (mean age: 62.7 years, SD: 15.2, median: 64 years) in fiscal year (FY) 2005 (year ending September 30, 2005). This is an ideal population in which to look at PDE-5 utilization. We extracted 2 fiscal years (2004-2005) of PDE-5 medication data and found 3,863,269 PDE-5 pharmacy claims dispensed for 547,255 male patients aged 18 years or older (mean: 61.5 years, SD: 10.5, median: 60 years). Sildenafil comprised 99.53% (N = 3,845,057) of all PDE-5 pharmacy claims followed by vardenafil at 0.46% (N = 17,643), and tadalafil at 0.01% (N = 569). The most commonly dispensed PDE-5 was sildenafil in 100 mg tablets accounting for more than 94% of all PDE-5 pharmacy claims and 95% of all sildenafil claims. As of January 15, 2006, following the aggregation of these data, the VHA was no longer purchasing sildenafil, and it has been replaced by vardenafil under a mandatory national contract.

Nearly 10.5% of the approximately 5.2 million male patients (aged 18 years or older) treated in the VHA were dispensed PDE-5 (547,255/5,200,120); this ranged from only 0.41% for those younger than 25 years (317/777,748) to 16.5% for those between the ages of 55 to 59 years (128,229/778,221). We found that 2.1% of PDE-5 patients were aged 39 years or less, 74.0% were between the ages of 40 and 69 years, and 23.9% were 70 years or older. Of the 547,255 male PDE-5 patients, 57.4% were married, 41.6% were not married, and 1.0% responses were unknown.

There were 12,984,875 tablets dispensed for 3,863,762 pharmacy claims, with a combined drug and dispensing cost of approximately $61.8 million, or $4.76 per tablet over 2 years (VHA annual pharmacy budget in 2005 of $5.4 billion). The average number of whole tablets per patient over the 2 years was 24 (range: 11 tablets for those younger than 25 years to 25 tablets for those between the ages of 50 to 54 years). Also, 36.8% of all utilization involved men aged 65 years or older, while 23.9% were aged 70 years or older.

The prevalence of PDE-5 use over the 2-year study period was 105.2 patients per 1,000 male veterans aged 18 years or older, approximately twice the prevalence of PDE-5 use (54.1 patients per 1,000 males aged 18 year or older) reported by Cooke et al. in their examination of a large managed care organization in the mid-Atlantic states in 2001. In that study, only 5% of PDE-5 patients were reported over the age of 70. In the United Kingdom, the addition of an oral agent to the available therapies for erectile dysfunction (ED) in 1998 led to a rapid rise in PDE-5 use that reached a plateau after 12 to 15 months at 3.47 patients per 1,000 adult males.

When compared with utilization data from other health care systems, a greater proportion of men in the VHA are dispensed PDE-5 drugs. The reason for this is unclear, but is likely multifactorial. Differences in commercial advertising, cost-entitlement benefits, comorbidities, and demographic profile likely contribute to this variation. Impotence is the most common condition attributable to direct-to-consumer advertising (DTCA), accounting for 16% of DTCA physician visits. The commercial marketing of ED drugs (e.g., “Ask your doctor if a prescription of Viagra is right for you” or “The Cialis promise program”) may increase demand for these medications beyond their intended clinical indications.

In response to the direct marketing of sildenafil to patients, the VHA chief patient care services officer in 1999 requested information on the effectiveness of treatments for ED to guide VHA recommendations. At that time, sildenafil was not on the national formulary or any Veteran Integrated Service Network (VISN) formulary. However, VHA physicians could prescribe sildenafil using local off-formulary procedures in accordance with the VHAS guidelines on ED treatment.

In spite of published guidelines for diagnosing and treating ED in veterans, obtaining a reliable measure of actual clinical ED in veterans is difficult and may vary across socioeconomic and cultural dimensions because of the potential stigma associated with this diagnosis. Medication safety concerns with PDE-5 drugs in the VHA are not driven as much by the prevalence of a disease as they are by the prevalence of medication usage. The large number of men over the age of 70 in the VHA taking PDE-5 raises concerns over safety since this group is known to be at high risk from multiple drug interactions and have a high burden of chronic disease.

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