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Aviation artist and pilot Sam Lyons says that his passion for creating airplane paintings comes from his love of flying. He paints every type of aircraft: antique, classic, military, commercial, and private. Lyons is known for his photorealistic style that makes viewers utter almost as many “oohs” and “aahs” as they would at an actual airshow. In fact, his paintings are often mistaken for photographs.

Lyons was born and raised in Atlanta, Georgia, and he credits his father—a B-24 pilot during World War II—with sparking his early interest in aviation. He graduated from Georgia Military Academy (now known as Woodward Academy), a private K-12 school in Atlanta, and subsequently enrolled at nearby Presbyterian College. Lyons obtained his private pilot-glider license while he was in college. After graduating with a bachelor of science degree in biology, he served 2 years as an officer in the U.S. Army, stationed at Edgewood Arsenal near Baltimore, Maryland. Following his stint in the Army, Lyons took a job as a teacher at Woodward Academy, where he taught 8th grade physical science and 9th grade biology for 4 years.

Lyons’ longtime avocation of airplane modeling led him to his next career as the owner of a hobby shop called Historical Hobbies. As his reputation as an expert model builder grew, he found himself in demand for custom projects. He also won many national modeling awards during this time. Always looking for a new challenge, Lyons decided to try his hand at painting, choosing Photorealism as his preferred method. By 1985, he had become so successful as an artist that he closed the hobby shop to the realism of filming. Lyons’ images have appeared on the covers of numerous magazines and catalogs, and he has also been commissioned to create works of art for various individuals, organizations, and corporations. The list includes U.S.A.F. Brigadier General C.W. Taylor, Barron Hilton of the Hilton Hotels Corporation, Dobbins Air Reserve Base, the U.S. Parks Department, Lockheed Martin Corporation, AT&T, and the Danbury Mint.

A 1942 patriotic-themed Super Stearman biplane is the star of Lyons’ stunning Airshow painting. He has created such a realistic image that one can just about hear the roar of the vintage airplane engine. Many detailed elements contribute to the realism of Airshow, including the B-25 Mitchell Bomber and P-51 Mustang planes in the distance, the colorful tents on the ground, and the group of spectators gazing skyward. “I often use a brush as fine as a human hair to paint the tiny details,” he explains. Lyons’ skillful use of perspective in this picture makes it look like the pilot is flying the Super Stearman high above the earth, gaining altitude for his next aerial maneuver. The composition’s diagonal airstrip forms an “X” with the opposing line of the plane/exhaust, further emphasizing the aircraft and pilot. (An interesting side note: All of the airplanes depicted in Airshow belong to Lyons’ friends who kept asking him, “When are you going to paint my plane?”)

Although most of his work focuses on aviation, he also paints portraits, landscapes, florals, automobiles, and boats. Lyons is a sculptor as well; he has created several impressive statues of historical aviation dignitaries.

Lyons will be inducted into the Georgia Aviation Hall of Fame in February 2009, becoming the first artist to be so honored. He joins the ranks of revered aviation figures such as Eddie Rickenbacker, Curtis Pitts, and Jacqueline Cochran.

You can find Lyons and his wife at their Lyons Studio booth every April during the Sun ‘n Fun Fly-In in Lakeland, Florida, and each July at the Experimental Aircraft Association AirVenture show in Oshkosh, Wisconsin. They encourage pilots, aviation enthusiasts, and anyone who is just “plane” crazy to take a tour of Lyons’ artwork on their Web site, www.LyonsStudio.com. One of the site’s highlights is the “Sam At Work” page, which shows the artist creating his Tuskegee Ace painting from start to finish.

Sheila Macho
Cover Editor

COVER CREDIT
Sam Lyons, Airshow, acrylic on canvas. Woodstock, Georgia. Copyright© 1989.

SOURCE
Interview with the artist.
JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients.

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  • tables and figures (generally no more than a total of 6). Submit referenced tables and figures on separate pages with titles (and, where appropriate) at the end of the manuscript, match symbols in tables and figures to explanatory notes, if included. May use 10-point type.
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REFERENCE

A Prospective Trial of a Clinical Pharmacy Intervention in a Primary Care Practice in a Capitated Payment System

Jeanette L. Altavela, PharmD, BCPS; Matt K. Jones, BA; and Merrilee Ritter, MS

ABSTRACT

BACKGROUND: There is evidence that pharmacist interventions improve clinical outcomes. The few studies that address economic outcomes (a) often report estimated instead of actual medical costs, (b) report only medication costs, or (c) have been conducted in settings that are not typical of community-based primary care.

OBJECTIVES: (a) determine whether a clinical pharmacist’s recommendations to physicians regarding optimizing medication therapy are related to medical costs in capitated patients in an internal medicine practice, and (b) compare what primary care physicians (PCPs) in a comparison group actually did proactively to optimize medication therapy versus what a clinical pharmacist would have recommended to them.

METHODS: This was a prospective, controlled study comparing 2 internal medicine practices. Study enrollment was performed using a screening process carried out every 1-2 weeks on a rolling basis for 1 year from July 2001 through June 2002. Eligibility criteria for prospective enrollment were (a) 1 or more risk factors: at least 1 chronic disease or an event (e.g., emergency room visit, adverse drug reaction, medication nonadherence) or aged 50 years or older, (b) a scheduled visit to see a PCP within 2 weeks from the screening date or a diagnosis of diabetes without a PCP visit during the first 6 months of the study, (c) need for optimization of medication therapy as determined by a clinical pharmacist on the screening date, and (d) 12 months of continuous insurance eligibility before enrollment in the study. For inclusion in the final study analyses, patients were also required to have continuous insurance eligibility through 12 months from study enrollment. One clinical pharmacist made recommendations to optimize medication therapy in the intervention group. For the comparison group, the same pharmacist proposed recommendations that remained concealed from the physicians. The primary outcome measure was per patient per year (PPPY) medical cost, based on plan liability (gross allowable costs minus patient costs), excluding prescription drug cost. Additional outcome measures included numbers of outpatient visits, hospital admissions, emergency room (ER) visits per 1,000 patients, and hospital days; and percent of recommendations that were accepted by the PCPs. Changes in outcome measures from the pre-intervention to post-intervention period were compared across study groups in a difference-in-difference analysis, using the Student’s t-test for normally distributed data and the Mann-Whitney U-test (nonparametric) for skewed data.

RESULTS: There were 127 and 216 adult patients in the intervention and comparison groups, respectively. The primary outcome, change in mean PPPY medical (excluding pharmacy) cost, did not differ significantly between the groups (P=0.711). The between-group difference in the change in ER visits per 1,000 patients approached statistical significance (P=0.054). Intervention group patients were more likely than comparison group patients to have the following issues addressed: medication nonadherence (85.7% vs. 40.0%, P=0.032), untreated indication (72.6% vs. 11.5%, P<0.001), suboptimal medication choice (60.0% vs. 5.9%, P<0.001) and cost-ineffective drug therapies (72.1% vs. 6.5%, P<0.001). Of the estimated number of actionable opportunities identified for the comparison group (but concealed from the physicians), 23.5% were adopted by comparison group physicians without any assistance from a clinical pharmacist.

CONCLUSION: Compared with patients of PCPs who received no input from a clinical pharmacist, patients of PCPs who received clinical pharmacist recommendations were more likely to have several medication-related issues addressed, including medication nonadherence, untreated indications, suboptimal medication choices, and cost-ineffective drug therapies. However, total medical (excluding pharmacy) costs for the intervention and comparison groups were not significantly different.

J Manag Care Pharm. 2008;14(9):831-43

What is already known about this subject
- Pharmacists can optimize medication therapy, resulting in improved patient outcomes, such as decreased exacerbations in patients with congestive heart failure and improved blood sugar management in patients with diabetes.
- Pharmacists are effective at recognizing potential and actual drug-related problems, such as drug-induced conditions and clinically relevant drug interactions.
- Pharmacist interventions can limit health care costs in specific groups of patients such as Medicaid and some health maintenance organizations.

What this study adds
- Patients in the intervention group were more than twice as likely to have medication nonadherence issues addressed (85.7% vs. 40.0%, P=0.032), 6 times as likely to have a medication prescribed that was indicated but not prescribed previously (72.6% vs. 11.5%, P<0.001), 10 times as likely to be prescribed an optimal medication for their condition (60.0% vs. 5.9%, P<0.001) and 11 times as likely to have their PCP prescribe more cost-effective therapies (72.1% vs. 6.5%, P<0.001).
- Of the estimated number of actionable opportunities identified by the clinical pharmacist for the comparison group but concealed from physicians, 23.5% were adopted by physicians without any intervention, whereas 76.5% were not adopted.
- The intervention and comparison groups did not significantly differ with respect to the study’s primary outcome, change in per patient per year (PPPY) medical cost excluding costs for prescription medications (P=0.711). From the pre-intervention to post-intervention period, mean PPPY medical costs declined by 15.1% in the intervention group and increased by 39.7% in the comparison group, however, median 12-month costs increased in both study groups, from $1,045 to $1,411 in the intervention group and from $1,130 to $1,638 in the comparison group.
Studies have shown that pharmacist consultation programs can improve clinical outcomes by optimizing medication use in ambulatory patients. Among patients in a heart failure clinic, a program of pharmacist evaluation (medication evaluation and recommendations, patient education and follow-up telemonitoring) resulted in a significant decrease in heart failure events and all-cause mortality. Study authors attributed this result to closer follow-up and optimizing doses of angiotensin-converting enzyme (ACE) inhibitors. In 2 randomized trials of patients with hypertension, those who were treated collaboratively by physicians and pharmacists achieved better control of blood pressure than did those who were managed by the physician alone. The physician-pharmacist team in 1 study increased medication optimization by titrating doses more effectively, switching to less expensive or more appropriate formulations of medications, and increasing appropriate laboratory monitoring. Even when patients’ medications were not changed, blood pressures were still improved. The authors speculated that improved medication adherence and beneficial education about hypertension contributed to these outcomes. Collaboration between physicians and pharmacists has resulted in a higher rate of patients meeting their lipid-level goals than previously achieved without collaboration in the same practice. The Asheville Project demonstrated that close collaboration between community pharmacists and patients with diabetes mellitus was associated with improved blood sugar management.

The National Committee for Quality Assurance’s key program for quality measurement is the Healthcare Effectiveness Data and Information Set (HEDIS). Since 2007, HEDIS has included measures of health care efficiency in the cost of care, referred to as “relative resource use” for chronic conditions. For example, asthma and cardiovascular conditions are measured both for quality, such as appropriate medication use and medication adherence, and for the cost of care. Some studies of clinical pharmacist activities have concentrated on lowering medication costs, but few have attempted to look at the impact on medical health care costs and utilization. Lowering medication costs has been accomplished by simplifying medication regimens, recommending less expensive alternatives, and providing pharmacotherapy consultation directly to patients. In an effort to decrease medical health care costs and utilization, some studies have demonstrated that pharmacists effectively identify potential and actual drug-related problems, potentially resulting in cost avoidance.

Previous studies that assessed clinical or medical cost outcomes were either conducted in U.S. Department of Veterans Affairs (VA) systems, in a setting where the patient was seen at a separate pharmacist visit, in a pharmacist-run clinic, or in populations that were dissimilar to general primary care internal medicine practices. Although these studies describe effective models, they do not extrapolate well to the typical primary care, internal medicine practice where medical patients are most often seen by physicians and in which pharmacists typically have no access to pertinent medical information (e.g., medical history, progress notes, laboratory and other test results, and consult notes) necessary to make clinical recommendations to prescribers. Embedding a clinical pharmacist within the primary care practice can remove those barriers.

In the 2 years before the present study, 2 clinical pharmacists working for the Greater Rochester Independent Practice Association (GRIPA) had gained experience with a number of primary care physicians (PCPs) on how to improve medication use and prevent the known hazards associated with medication misuse in their patients. GRIPA is a unique partnership of more than 600 physicians and 2 hospitals in 2 counties in western New York. The pharmacists were located within the physician practice with little disruption to the normal office workflow. At that time, the pharmacists did not meet with the patients, but provided written recommendations to each patient’s physician. The clinical pharmacist had opportunities to affect a patient’s medication adherence, to ensure that the most appropriate medications were both prescribed and monitored appropriately, and to help prevent therapeutic duplication and adverse drug reactions. In addition, pharmacists served as a dynamic drug information resource for the physician. For patients whose care was affected by the clinical pharmacist’s recommendations, a trend toward lowered medical health care costs and utilization was observed. However, no comparison group of patients without the services of a clinical pharmacist was available at that time.

The primary purpose of the present study was to determine whether the recommendations of a clinical pharmacist embedded in a primary care practice, which had not previously received services from GRIPA’s clinical pharmacists, would decrease the medical costs of capitated patients. The secondary purpose of the study was to compare actions taken by physicians in a comparison group, which received no pharmacist input, with actions taken by physicians who were provided recommendations by a clinical pharmacist.

### Methods

#### Study Setting

This was a prospective, controlled study conducted in 2 primary care practices located in the suburbs of Rochester, New York. One practice served as the intervention group, and the other served as the comparison group. Physicians at both practices were members of GRIPA and had never received services from GRIPA’s clinical pharmacists. ViaHealth, GRIPA’s parent company, owns 2 hospitals and one-half of GRIPA; the physicians own the other half. GRIPA operates under financial risk contracts with insurance companies. A portion of the patients in these primary care practices were members of an insurance company with which GRIPA had a risk contract. The patients were enrolled in either the insurance company’s commercial insurance plan or its Medicare insurance product. The risk contract provided GRIPA with an incentive to proactively optimize medical care to...
The second criterion served to identify patients with diabetes claims but no PCP visit during the first 6 months of the study.

The intervention group practice had 957 capitated patients, and the comparison group practice had 1,272 capitated patients, with 12.3% and 31.6% enrolled in the Medicare insurance product, respectively. The remaining capitated patients in each group were enrolled in the commercial insurance product. Both practices consisted of internal medicine physicians, with 2 physicians in the intervention group and 4 physicians in the comparison group. The intervention group was privately owned, whereas the comparison group was owned by ViaHealth. Both practices used paper-based medical records and appointment scheduling systems. The 2 physicians in the intervention group had practiced for 18 and 6 years, respectively, whereas the 4 physicians in the comparison group had been in practice for 20 years on average (range 17-25 years).

One clinical pharmacist worked within both practices and brought a laptop computer to record her activity in a secure database. At the intervention group practice, the pharmacist did not have Internet access. The comparison group practice was equipped with computers with limited Internet access, which the pharmacist could use if needed. The clinical pharmacist recorded medication recommendations that were either provided to physicians (intervention group) or concealed (comparison group).

Written informed consent was obtained from the physicians at both practices. The ViaHealth Clinical Investigations Committee (institutional review board) approved this study.

**Patient Selection**

Patients enrolled in this study were continuously enrolled in 1 of the 2 contracted insurance products (commercial or Medicare) for the entire 12 months before their study enrollment date to ensure that there were complete baseline claims data. The patient selection period, during which patients were entered into the study in a rolling screening and enrollment process conducted by the clinical pharmacist every 1-2 weeks, began on July 1, 2001, and ended on June 30, 2002. Patient membership status was provided to the pharmacist at study initiation, and insurance claims were used to determine each patient’s risk factors, which were used as part of the entry criteria in the study (Table 1). To be eligible for enrollment into the study, patients had to be scheduled for an appointment with a PCP within 1-2 weeks of the screening date or have a diagnosis of diabetes mellitus documented in their claims but no PCP visit during the first 6 months of the study. The second criterion served to identify patients with diabetes mellitus that did not have optimal follow-up care. Patients identified on the appointment schedule had to meet at least 1 of the following 2 criteria: (a) 1 or more of the risk factors listed in Table 1, identified through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG), or Current Procedural Terminology (CPT) codes found in each patient’s insurance claims for the 12 months before April 2001, or (b) absence of any of the above risk factors, but aged 50 years or older. Finally, a need for medication optimization was required for study entry; patients meeting the other study criteria were enrolled only if the clinical pharmacist recorded recommendations to optimize medication therapy, whether reported to the PCP (intervention group) or concealed (comparison group).

Each patient’s study enrollment date was the first date on which the pharmacist made a recommendation for that patient. Post-enrollment follow-up lasted 12 months for each patient. Thus, to be included in the final study analyses, the patient had to maintain continuous insurance eligibility and remain in the care of the same PCP for the 12 months after the study enrollment date. Insurance eligibility was determined by a monthly membership roster sent to GRIPA from the insurance company. The membership status and risk factor evaluation of the patients in the physician practices were updated in January 2002.

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**TABLE 1**  
Risk Criteria for Study Entry: Hospital and Medical Claim Codes

<table>
<thead>
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<th>Condition</th>
<th>ICD-9-CM</th>
<th>DRG</th>
<th>CPT</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>250.XX</td>
<td>294.295</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>428.XX</td>
<td>115, 124, 125, 127</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>410-410.9, 411.XX, 412-414XX, (Except 414.1, 414.10, 414.11, or 414.19)</td>
<td>106, 107, 109, 112, 116, 121, 122, 123, 132, 140</td>
<td>33510-33545</td>
</tr>
<tr>
<td>Asthma</td>
<td>493.XX</td>
<td>096.097</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>491-492.XX, 493.2, 496.XX</td>
<td>888</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>401-405.XX</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>272.XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>346.XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>427.31, 427.32</td>
<td>138, 139</td>
<td></td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>995, 995.1, 995.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncompliance with medical treatment</td>
<td>V15.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any emergency room visit</td>
<td></td>
<td></td>
<td>99281-99285</td>
</tr>
<tr>
<td>Tobacco abuse disorder</td>
<td>305.1, 989.84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Description of the Intervention

In both practices, the same clinical pharmacist reviewed each patient’s medical record and assessed whether the patient’s medication therapy could be optimized. For the intervention group, the clinical pharmacist provided the PCP with written recommendations (consult note) regarding drug-related problems similar to those described by Strand et al.17 All consult notes were completed before the patient’s appointment with the PCP. The consult notes were not meant to be a permanent part of the medical record and were labeled accordingly, which likely limited physicians’ potential concerns about medical malpractice or liability related to these notes. The consult notes were written on colorful paper and placed conspicuously in the paper medical record.

For the comparison group, the clinical pharmacist documented in the database the recommendations for each patient, which remained concealed from the PCP; physicians in the comparison group practice were asked to “act as though the clinical pharmacist present in the office is invisible.” The estimated number of actionable opportunities for the comparison group was (a) calculated by multiplying the recommendation acceptance rate for the intervention group (the percentage of clinical pharmacist recommendations that were actually adopted by intervention physicians) times the number of concealed recommendations for the comparison group, and then (b) compared with the actual number of changes made by comparison group physicians without clinical pharmacist assistance. The pharmacist also documented in the privacy-secured database all known chronic diseases and other demographic information for both study groups, including height and weight, if these data were available in the medical record.

Medical record reviews were conducted for all patients who were enrolled in the study. The medical record included medical history, physical exam, consult notes, laboratory data, and other test results. For 72.9% and 39.3% of the capitated patients in the intervention and comparison group, respectively, the pharmacist had access to claims data reflecting the patient’s prescription refill (pharmacy) claims from the patient’s insurance company. Pharmacy claims data were available only for the capitated patients that had a prescription benefit through the insurance company with which GRIPA had a risk contract. For instance, there were no pharmacy data on patients who had medical insurance but filled all their prescriptions through the VA. None of the physicians had direct access to the pharmacy claims data. The pharmacist interpreted the pharmacy claims data and distilled that information into her consult notes as needed to optimize medication therapy. However, because pharmacy data were not available for all study patients, costs for prescription drugs could not be assessed except in the aggregate.

In addition to providing proactive recommendations to the intervention group physicians, the clinical pharmacist was available to help with any medication-related problems or drug information issues at the physicians’ or staff’s request. The clinical pharmacist also offered physician education, patient counseling, adherence monitoring and education as deemed appropriate. Patient counseling was done only on an as-needed basis, was not directed at any particular condition, and generally dealt with medication nonadherence. Otherwise, most of the medication adherence issues were simply brought to the attention of the PCPs for them to address during the patient’s visit.

The clinical pharmacist was not available to the comparison group physicians for consultation during the study period. However, an a priori decision was made that, if a significant finding were discovered during a medical record review in the comparison group that required immediate attention to prevent patient harm, the clinical pharmacist would consult the physician and the patient would be discontinued from the study.

The clinical pharmacist recorded physician responses to each recommendation at 6 months and 12 months after the recommendation was made, in both the intervention and comparison groups. Recommendations made by the pharmacist that were no longer applicable by the time of the patient’s appointment were excluded from the analysis. The clinical pharmacist recorded a physician response as “accepted” if there was evidence documented within the medical record indicating that the recommendation was followed (e.g., a change in a prescription, a laboratory test ordered).

Once patients met all criteria for inclusion, the study was conducted with an intent-to-treat analysis. Whether or not the physician adopted the pharmacist’s recommendation, that patient was included in the final analysis.

Outcome Measures

Medical costs and utilization were obtained from medical claims data contained in the GRIPA data warehouse. These data originated from each enrolled patient’s insurance company. Cost (plan liability) was calculated as a per patient per year (PPPY) amount for the primary outcome and tabulated for all claims for hospitalizations, emergency room (ER) visits, radiology and laboratory tests, PCP visits, and specialty visits. Although included in medical costs, inpatient costs also were tallied separately. The utilization data included number of hospitalizations, ER visits, PCP visits and specialty visits, and hospital length of stay in days. Hospitalizations were identified by any claim with a valid diagnosis related group or a revenue code between 100 and 219 (room and board) as long as the facility type was not a skilled nursing facility or nursing home. Medical costs and utilization were determined for 12 months before and after each patient’s enrollment date.

Prescription cost data were available only in aggregate as a one-time report provided by the insurance company. Investigators did not have access to complete prescription medication claims data because GRIPA was not at financial risk for medication...
expenses. Thus, no patient-level analyses of prescription data were performed.

Episode Treatment Groups (ETGs) for each group were not available at the start of the study but were calculated based on historic information before study analysis was completed. ETGs identify and quantify an episode of care that spans inpatient, outpatient, and all ancillary services, including pharmaceuticals, and takes into consideration patient age and comorbidities. ETGs were believed to be important to include in the study analyses to determine the degree of similarity of the 2 groups throughout the study because ETGs are a clinically useful tool to measure health care demand.

Statistics
Before the study, interest had been expressed in looking at the response variables by different age groups as well as over the entire population, because published studies about clinical pharmacist interventions have typically been in patients with chronic disease and often in older age groups. Two subgroups—age 65 or younger versus older than age 65—were compared. Other subgroups were created for 3 age categories—20-50 years, 51-65 years, and older than age 65—and the data for these 3 subgroup populations were analyzed separately.

Categorical data (e.g., rates, percentages) were analyzed using the likelihood ratio chi-square test for differences in proportions, comparing the intervention group and comparison group. The variables analyzed included sex, age category, weight category, and presence or absence of comorbidities and risk factors including congestive heart failure (CHF), diabetes mellitus, coronary artery disease (CAD), asthma, chronic obstructive pulmonary disease, and current cigarette smoking.

Continuous data were examined, using histograms and scatter plots, to determine distribution characteristics and relationships with other variables. Normally distributed data were analyzed using Student's t-tests for 2-group differences. Non-normally distributed data were analyzed using the Mann-Whitney U-test, which is a nonparametric test for 2-group comparisons. Baseline variables analyzed with these methods included age, ETGs, and body mass index (BMI). Study outcome measures were assessed using a difference-in-difference analysis by subtracting pre-intervention values from post-intervention values and comparing the change amounts by study group.

Statistical significance was determined using an alpha level of 0.05. Statistical analysis was performed using the Minitab version 13.32 (Minitab Inc., State College, PA) and SPSS versions 13.0 and 14.0 (SPSS Inc., Chicago, IL) statistical packages.

■ Results

Study Enrollment
Counts of eligible patients who were enrolled between July 2001 and June 2002, patients excluded, and patients included in the final data set are shown in Figure 1. More than 80% of the enrolled patients met more than 1 risk factor determined from insurance claims (data not shown). Two percent of the enrolled patients were identified because they had a diagnosis of diabetes with no scheduled appointment during the first 6 months of the study. The only patient in the comparison group with a significant finding that required the clinical pharmacist to make an urgent recommendation to the comparison group physician was excluded for not having 12 months of continuous insurance eligibility after study enrollment. Thus, no patients in the comparison group were discontinued from the study solely because of clinical pharmacist interaction with the comparison group physicians. Of patients who met all the criteria for enrollment in the prospective phase of the study (i.e., of those who were assigned to either the intervention group [n = 159] or the comparison group [n = 290]), exclusions for failure to maintain continuous insurance eligibility were made for 30 (18.9%) of intervention group and 71 (24.5%) of comparison group subjects.
Demographics

Patient demographics at study enrollment are shown in Table 2. The mean [SD] age of patients in the intervention group (59.6 [11.6]) was younger than in the comparison group (68.2 [12.7]; P<0.001). There was a nonsignificant (P=0.068) trend toward lower rates of CAD in the intervention group (14.2% and 22.2% for intervention and comparison groups, respectively). The prospective risks (ETGs) for each age group were similar. The intervention group had a higher proportion of morbidly obese patients than did the comparison group (12.7% vs. 4.8%, respectively; P=0.009).

In conducting analyses for the 3 age groups shown in Table 2, the greatest attention was given to the largest group of patients (older than 65 years of age), though the data are not shown. Among patients older than 65 years of age, the mean age was younger in the intervention group (72.3) than in the comparison group (75.6), and the comparison group had a higher proportion of patients older than 80 years of age. Also, among patients older than 65 years of age, the BMI, selected disease conditions, and ETGs were similar between the intervention and comparison groups. Because of the small number of patients in the other 2 age groups, results for these age groups are not presented in this report. However, these results are available from the primary author by request.

Primary and Secondary Outcomes

All Patients: Mean (SD) Pppy medical costs (excluding costs for prescription medications) declined by 15.1% ($755) in the intervention group, from $4,995 ($15,774) pre-intervention to $4,240 ($11,391) post-intervention, and increased by 39.7% ($1,435) in the comparison group, from $3,616 ($8,256) to $5,051 ($14,862; Table 3). Median 12-month costs increased in both study groups, from $1,045 to $1,411 in the intervention group and from $1,130 to $1,638 in the comparison group. The
intervention and comparison groups did not differ with respect to the study's primary outcome, change in PPPY medical cost ($0.711).

Secondary outcomes are displayed in Table 4. Both before and after the intervention, intervention group patients had a lower average number of PCP visits than did comparison group patients. However, the between-group difference in the mean change in PCP visits from pre-intervention to post-intervention was not statistically significant ($P=0.914$). From the pre-intervention to the post-intervention periods, hospital admissions per 1,000 patients increased from 206.0 to 221.0 (7.3%) in the intervention group and from 121.0 to 204.0 (68.6%) in the comparison group, although the between-group difference in the amount of change from pre-intervention to post-intervention did not reach statistical significance ($P=0.329$). ER visits per 1,000 patients declined by 44.1% in the intervention group (from 127.0 to 71.0) and increased by 57.6% in the comparison group (from 144.0 to 227.0); the between-group difference in the change amounts approached statistical significance ($P=0.054$).

Prescription cost was compared at an aggregate level, with no statistical analyses available. The intervention group's prescription claims cost (insurance plan liability) increased by 17.4% (from $105,000 to $123,227), whereas the comparison group's prescription claims cost decreased by 10.1% (from $90,135 to $81,042).

Patients Older Than 65 Years of Age: For patients older than 65 years of age, study groups did not significantly differ with respect to the study's primary outcome, change from pre-intervention to post-intervention in medical costs (data not shown). However, the intervention group's average PPPY cost increased 29.7%, whereas the comparison group's cost increased 65.8% from before to after the intervention. ER visits decreased by 1.6% in the intervention group and increased by 60.4% in the comparison group.

Clinical Pharmacist Interventions: The clinical pharmacist made 271 recommendations to the intervention group with an average of 2.1 recommendations per patient versus 286 concealed recommendations for patients in the comparison group with an average of 1.3 per patient. In the intervention group, 189 (69.7%) of the recommendations were accepted, whereas 47 (16.4%) of the concealed recommendations were acted on by comparison group physicians. Thus, assuming that about 70% of the concealed (comparison group) recommendations were actionable (i.e., would have been acted upon by the comparison group physicians if the recommendations had been made and not concealed), comparison group physicians identified 47 of 200, or about 23.5%, of actionable opportunities on their own without the services of a clinical pharmacist.

Figure 2 shows broad categories of recommendations accepted in the intervention group resulting in more optimal care for those patients. Table 5 provides specific examples of recommendations within these broad categories. Intervention group patients were more than twice as likely as comparison group patients to have medication nonadherence issues addressed (85.7% vs. 40.0%, $P=0.032$), and 6 times as likely to have a medication prescribed that was indicated but not prescribed previously (72.6% vs. 11.5%, $P<0.001$). Among patients at risk for cardiovascular events, intervention group patients were more than 8 times as likely as comparison group patients to be started on daily aspirin (90.9% vs. 11.1%, $P<0.001$; data not shown in figure) and more than 7 times as likely to receive pneumonia vaccination as recommended by the Centers for Disease Control and Prevention (76.9% vs. 10.0%, $P<0.001$; data not shown in figure). Intervention group patients

### Table 3: Cost Outcomes in the 12 Months Before and After Study Enrollment Date

<table>
<thead>
<tr>
<th>Cost Outcomes</th>
<th>Intervention Group</th>
<th>Comparison Group</th>
<th>$P$ Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean [SD]</td>
<td>Median</td>
</tr>
<tr>
<td>Total medical cost$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPPY before</td>
<td>$1,045</td>
<td>$4,995 [157,774]</td>
<td>$1,130</td>
</tr>
<tr>
<td>PPPY after</td>
<td>$1,411</td>
<td>$4,240 [113,911]</td>
<td>$1,638</td>
</tr>
<tr>
<td>PPPY difference</td>
<td>$238</td>
<td>$-755 [156,17]</td>
<td>$257</td>
</tr>
<tr>
<td>Percent change</td>
<td>-15.1%</td>
<td></td>
<td>39.7%</td>
</tr>
<tr>
<td>Inpatient cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPPY before</td>
<td>$0</td>
<td>$2,090 [129,83]</td>
<td>$0</td>
</tr>
<tr>
<td>PPPY after</td>
<td>$0</td>
<td>$1,415 [76,65]</td>
<td>$0</td>
</tr>
<tr>
<td>PPPY difference</td>
<td>$0</td>
<td>$-675 [156,96]</td>
<td>$0</td>
</tr>
<tr>
<td>Percent change</td>
<td>-32.3%</td>
<td></td>
<td>18.2%</td>
</tr>
</tbody>
</table>

$^a$M-W = Mann-Whitney U-test; the Mann-Whitney U-test for independent 2-sample groups was used when the continuous variables were not normally distributed.

$^b$Total medical cost excluding outpatient pharmacy costs. Cost outliers were not removed from this analysis and ranged from a decrease of $1.8 million for 1 patient in the intervention group to an increase of $1.7 million for another patient in the comparison group and were attributable to hospitalizations for cancer treatments, congestive heart failure, and major surgeries, including 1 liver transplant.

Cost = plan sponsor costs (gross allowable minus patient costs); PPPY = per patient per year.
were 10 times as likely to be prescribed an optimal medication for their condition (60.0% vs. 5.9%, P < 0.001) and more than 11 times as likely to be prescribed more cost-effective therapies (72.1% vs. 6.5%, P < 0.001).

**Discussion**

This study demonstrated that embedding a clinical pharmacist to work within a primary care physician’s office benefits patient care and that physicians readily adopt opportunities to optimize medication therapy when they are provided with clinical pharmacist recommendations. Although the difference in medical costs between the intervention group and the comparison group was not statistically significant, a nonsignificant trend suggests that the intervention may have had a positive effect on medical costs and warrants further investigation with a larger sample size. The trend in patients older than 65 years of age revealed that the average PPPY cost increased by 29.7% for the intervention group, compared with 65.8% for the comparison group, but again this difference was not statistically significant.

To our knowledge, the current study is the first to demonstrate in detail the types and frequency of opportunities to improve medication therapy by physicians who were not provided with clinical pharmacist interventions. This study showed that physicians appear to act on only about one-quarter of these opportunities when they are without the assistance of a clinical pharmacist.

The Impact of Managed Pharmaceutical Care Resource Utilization and Outcomes in Veterans Affairs Medical Centers (IMPROVE) study of an older high-risk population described similar increases in PPPY health care costs for both the intervention group (20.7%) and the comparison group (29.7%).

The PPPY cost in the IMPROVE study was calculated differently, in that it included the cost of the pharmacist’s cognitive services and medications and relied on estimated medical costs for the primary outcomes. Many other studies presenting medical health care cost outcomes have also been based on estimated costs, whereas fewer studies used actual costs.
We were unable to assess differences in drug cost between the intervention group and comparison group in the present study because study enrollment criteria did not require that patients had prescription drug coverage during any part of the study. The insurer did not grant access to individual prescription medication financial data because GRIPA was not at risk for medication costs. However, aggregated pharmacy claims cost data suggested an increased cost in the intervention group. This cost finding is similar to those of other similar studies in which the pharmacists had access to the patients’ medical records and did not limit pharmacist services to one disease state. These studies showed a trend of slightly higher annual cost of prescription medication (5.7%-8.6%) in the intervention groups. In the present study, despite the clinical pharmacist’s ability to lower the cost of some medications, one of the most common recommendations was to start a new medication when it was indicated but previously overlooked by the physician. This pattern potentially increased medication cost. The intervention group was 6 times as likely as the comparison group to have a new medication started. Some medications initiated during the study were calcium and vitamin D supplements for the prevention or treatment of osteoporosis, or daily aspirin for patients with diabetes mellitus, which would not be expected to change the overall prescription medication costs. However, other medications were initiated to treat hyperlipidemia, provide ACE inhibitors for patients diagnosed with diabetes mellitus or CHF, or assure that CAD patients had fresh sublingual nitroglycerin.

Unique to this study was that outcomes for “usual care” with regard to medication management were documented and compared with outcomes for the intervention in a primary care practice. This design provided greater understanding of what might have potentially been accomplished for the patients receiving usual care, had they received the services of a clinical pharmacist. Figure 2 shows that many potential opportunities appeared to exist for physicians to optimize medication therapy. Hanlon et al. also recorded concealed recommendations for a randomized

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Figure 2: Percentage of Optimal Care Opportunities Accomplished

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Intervention</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untx Indication</td>
<td>62.78</td>
<td>0.0%</td>
</tr>
<tr>
<td>Cost</td>
<td>43.31</td>
<td>10.0%</td>
</tr>
<tr>
<td>Optimal Drug</td>
<td>15.34</td>
<td>20.0%</td>
</tr>
<tr>
<td>ADR</td>
<td>14.27</td>
<td>20.0%</td>
</tr>
<tr>
<td>Non-Adherence</td>
<td>14.10</td>
<td>20.0%</td>
</tr>
<tr>
<td>Drug Monitoring</td>
<td>10.11</td>
<td>20.0%</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>8.13</td>
<td>10.0%</td>
</tr>
<tr>
<td>Sub Dose</td>
<td>4.4</td>
<td>20.0%</td>
</tr>
<tr>
<td>Supra Dose</td>
<td>2.6</td>
<td>10.0%</td>
</tr>
<tr>
<td>No Indication</td>
<td>2.5</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*Numbers below the recommendation category represent the total number of recommendations for the intervention group and comparison group respectively. P values were determined from likelihood ratio chi-square test. ADR = adverse drug reaction; Sub = subtherapeutic; Supra = supratherapeutic; Untx = untreated.
Specific Examples of Optimal Care Opportunities

<table>
<thead>
<tr>
<th>Description of Optimum Care Intervention Type</th>
<th>Examples of Recommendations:</th>
</tr>
</thead>
</table>
| Untreated indication: Recommendation to start a medication for a medical condition that is currently untreated but considered a standard of care | - Statins for patients with coronary artery disease and low-density lipoprotein cholesterol above goal  
- Angiotensin-converting enzyme inhibitor for patient with diabetes and microalbuminuria |
| Cost: Recommendation for an equally effective but less expensive medication | - Use one-half tablet of a higher strength tablet of the same medication to achieve the dose (e.g., 80 mg of atorvastatin, one-half tablet daily, instead of 40 mg of atorvastatin daily).  
- Change prescription to 1 tablet of a higher strength instead of multiple tablets of lower strength to achieve the dose (e.g., 40 mg of atorvastatin twice daily to 80 mg of atorvastatin once daily). |
| Optimal drug: Recommendation to replace a current medication with a more appropriate medication based on patient characteristics, comorbidities, and pharmacokinetic or other characteristics of the medication | - Glipizide is preferred over glyburide in patient aged 71 years with chronic kidney disease.  
- Switch from a long-acting benzodiazepine (flurazepam) to a shorter-acting benzodiazepine such as oxazepam in elderly patient with insomnia. |
| Adverse drug reactions: Identification of a potential or actual adverse drug reaction | - For patient with prostate cancer on leuprolide acetate, consider calcium and vitamin D administration and bone density test because there is bone loss associated with administration of leuprolide.  
- Avoid pioglitazone or rosiglitazone in patient with stage 3 congestive heart failure. |
| Nonadherence: Evidence that the patient is not taking the medication as prescribed | - Address nonadherence with patients with osteoporosis who have stopped filling their prescription for alendronate.  
- Address nonadherence with a patient prescribed a statin whose cholesterol has increased dramatically yet not been addressed at previous appointments. |
| Drug monitoring: Identification of inappropriate medication monitoring and recommending appropriate medication monitoring | - Order a serum potassium determination for patient started on hydrochlorothiazide more than 1 year ago.  
- Order thyroid-stimulating hormone determination for patient with change in levothyroxine dose more than 3 months ago who does not have current blood work done. |
| Drug interactions: Identification of clinically relevant drug interactions or warning of potential drug interactions | - Assure that patient treated for hypothyroidism and starting on calcium supplement does not take calcium and levothyroxine together.  
- Limit acetaminophen dosing to less than 2 gm per day in patient on chronic carbamazepine, which can induce acetaminophen conversion to toxic metabolite. |
| Subtherapeutic dose: Recommendation for alternative dosing for someone on a subtherapeutic dose | - Increase angiotensin-converting enzyme inhibitor dose to goal dose per congestive heart failure standards.  
- Increase calcium and vitamin D supplement to achieve recommended total daily intake. |
| Supradose: Recommendation for alternative dosing for identification of a patient prescribed a dose that is inappropriately high or should ideally be titrated downward | - Starting dose of niacin extended-release tablets at 1,000 mg is unlikely to be tolerated by patient; suggest 500 mg at bedtime.  
- Patient taking conjugated estrogens, 0.9 mg daily—attempt titrating estrogen dose to minimum effective dose for postmenopausal symptoms. |
| No indication: Recommendation to discontinue a medication that appears to lack an indication | - Discontinue proton pump inhibitor in a patient recently discharged from hospital with new prescription for a proton pump inhibitor without a gastrointestinal condition.  
- Discontinue 1 mg folic acid daily supplement in a patient who discontinued oral methotrexate more than 1 year ago. |

control group and found that, similar to the present study’s results, 55.1% of intervention group and 19.8% of control group physicians enacted the clinical pharmacist’s recommended changes.27

In the present study, between-group differences in the rates of optimized medication therapy may have contributed to the trend in lower hospital admissions and ER visits for patients provided with clinical pharmacist services. For example, medication nonadherence, leading to poor disease control, also can lead to increased hospitalizations and can be an important driver of overall medical costs.28 Although findings of some studies call into question the relationship between improved medication adherence and clinical outcomes or health care costs,26,29 other studies have found a beneficial effect of adherence on clinical outcomes.20,30 Recognizing drug interactions and adverse drug reactions are part of the expertise of a clinical pharmacist and may have contributed to minimizing ER visits in the intervention group as evidenced in other settings.20,22,25 For example, the comparison group in the present study included a woman older than 80 years of age who was prescribed a low-dose tertiary
amine tricyclic antidepressant for suspected urge incontinence. Within weeks of starting this central nervous system active medication with anticholinergic activity, she suffered falls, resulting in hospitalization for fracture.

Unlike much of the published literature about health care systems such as the VA, this study took place in a typical primary care practice that did not have a common electronic medical record platform. This study also involved a privately owned medical practice that was not associated with either a pharmacy or medical school, unlike many of the studies conducted in ambulatory care pharmacist practice environments within the United States.1,2,9,21,31-33 The clinical pharmacist's approach used in the present study could potentially take place in any community, in any doctor's office, with little disruption to workflow. Space is a precious commodity in primary care practices; using this particular model would allow clinical pharmacists to work in any type of space and flex their schedule according to the needs of the medical practice.

In contrast to other studies, patients who may have needed the most help with medication therapy were not excluded.1,3,30,33 The IMPROVE study excluded patients who had a psychiatric illness requiring mental health services, poor understanding of written and spoken English, visual impairment and residence far from the physician office, or no working telephone.19 The only ability required for patients in the current study was ability to physically make it to a physician office visit; there were no other limits.

Limitations
First, the medical practices were selected, not randomized. Recruiting physicians to participate in the comparison group was a challenging task, as the comparison group physicians did not benefit from participating. The physicians in the present study's comparison group were likely willing to participate because they had an understanding of the valuable role of a clinical pharmacist; they had past experience working with clinical pharmacists who managed anticoagulation and provided monthly education sessions on medications within a health maintenance organization. Neither physicians in the same practice nor patients were randomized, which may have biased the results. However, it did prevent the contamination that could have occurred if a single physician had worked with both intervention and comparison patients. This contamination, although not ideal for a research study, is typically something that clinical pharmacists strive for within a medical practice. Ideally, after a clinical pharmacist makes a recommendation 2 or 3 times, the physician tends to apply this knowledge appropriately to the remainder of similar patients in his or her practice.

Second, there are major concerns about whether the patient cohorts were comparable, particularly because of the difference in age. The intervention group and comparison groups differed at baseline; of patients with 12 months of pre-intervention eligibility, 25.9% of intervention and 45.3% of comparison patients were aged 66 years or older. The percentages of study patients excluded from the final analysis for not having 12 months of continuous insurance eligibility following the date of study enrollment were similar in the intervention group (30 of 159 patients or 18.9%) and the comparison group (71 of 290 patients or 24.5%). However, just 15.6% of the excluded patients in the intervention group were aged 65 years or younger, compared with 66.2% in the comparison group. This pattern appeared to be a result of an insurance change to a self-insured product made by 1 large employer in Rochester during this study, thus removing its participants from the capitated population. The employer change excluded so many younger patients in the comparison group that the difference in mean age between the 2 groups became even larger.

Third, we made an a priori decision to exclude all patients that did not have 12 months of continuous insurance eligibility after study enrollment; thus it is unknown how the clinical pharmacist interventions affected those patients that subsequently either died or disenrolled from the insurance plan. Fourth, the medical cost data contained some outlier cases that were not removed from our study sample because of our a priori decision to retain all eligible cases for final analysis. There were no patients with trauma or motor vehicle accidents, but a very small number of patients in both the intervention and comparison groups had extreme changes in 12-month medical costs; these changes ranged from a decrease of $1.8 million for 1 patient in the intervention group to an increase of $1.7 million for another patient in the comparison group. These charges were attributable to hospitalizations for cancer treatments, congestive heart failure, and major surgeries including 1 liver transplant.

Fifth, the general application of the study findings could be affected by several factors. The 69.7% acceptance rate of recommendations by physicians was higher than in many published outpatient studies.23,24,26,34 This outcome may have been attributable to the use of only 1 person, the clinical pharmacist who performed the intervention, to determine the acceptance rate in each of the 2 study groups. However, the relationships built between the clinical pharmacist and physicians in the intervention group over the 12 months probably played a role in the success of the intervention as demonstrated in other studies in which authors surmised that interpersonal relationships between the pharmacist and physicians contributed to improved outcomes.2,30 Although the present study did not measure whether acceptance of recommendations resulted in resolution of the identified problems, the acceptances did reflect positive care decisions moving in the direction of resolution. The IMPROVE study authors stated that 69% of their recommendations were resolved, but when they removed the interventions performed directly by the pharmacist (without needing physician approval), their resolution rate declined to 57%.19
Sixth, the study may have underestimated the benefits of the clinical pharmacist because one of the comparison group physicians also was a member of a pharmacy and therapeutics committee for another large insurer in Rochester, New York, and was acutely aware of medication related problems and money-saving opportunities. The average number of recommendations per patient in the intervention group versus the comparison group (2.1 vs. 1.3, respectively) might also have contributed to study findings. Lastly, the inclusion criteria for this study were rather broad. As a result of our findings, we have narrowed the criteria for consultation, limiting our target population to the most high-risk patients with multiple comorbidities.

Conclusion

A clinical pharmacist can promote optimal medication therapy in outpatients by working with primary care physicians within their office practices. Although the medical (excluding pharmacy) costs of the intervention and comparison groups did not differ significantly, a nonsignificant trend suggests that the intervention may have had a positive effect on medical costs and warrants further investigation with a larger sample size.

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This research was not funded. The authors are employees of the Greater Rochester Independent Practice Association. Study concept and design were primarily the work of Altavela, and Altavela performed all of the data collection. Altavela and Ritter interpreted the data with assistance from Jones. Altavela wrote and revised the manuscript with some assistance from Ritter.

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REFERENCES

A Prospective Trial of a Clinical Pharmacy Intervention in a Primary Care Practice in a Capitated Payment System


Analysis of Costs Associated With Administration of Intravenous Single-Drug Therapies in Metastatic Breast Cancer in a U.S. Population

Gregory B. Kruse, MPH, MSc; Mayur M. Amonkar, PhD; Gregory Smith, BA; Dean C. Skonieczny, MBA, BSE; and Spyros Stavrakas, PhD

ABSTRACT

BACKGROUND: An estimated $8.1 billion (in 2004 dollars) is spent annually on total health care costs for the treatment of breast cancer in the United States. Breast cancer has traditionally been treated with intravenous (IV) cancer therapies that entail not only the drug acquisition cost, but additional costs of personnel time, supplies, and equipment used in the preparation and administration of the IV drug. A systematic study of the costs of IV administration in the metastatic breast cancer (MBC) population has not been performed.

OBJECTIVE: To assess the cost components, overall and by payer type and patient age group, for administering a single-agent IV breast cancer drug to women with MBC in the United States.

METHODS: Women diagnosed with MBC (ICD-9-CM codes 174.XX and 196.XX-198.XX) reported any time between January 1, 2003, and May 31, 2006, and receiving single-agent IV breast cancer therapy (including intramuscular fulvestrant) during a visit were identified (using HCPCS and CPT codes) from an administrative claims database supporting 46 general/oncology clinics in the United States. Study drugs were either FDA-approved for breast cancer or recommended for use as preferred single agents per National Comprehensive Cancer Network (NCCN) clinical practice guidelines for breast cancer. Costs were estimated using the contracted allowed payment, which is the amount that the provider is eligible to receive from all parties, including payers and patients. Costs were measured using 2 approaches—average cost per IV-administration visit and average cost per patient per month (PPPM).

RESULTS: Over the 41-month study period (through May 31, 2006), 46,273 patients had a breast cancer diagnosis, of which 8,533 (18.4%) were metastatic; 828 (9.7%) of these patients received 1 of 11 single-agent IV breast cancer drugs over 7,406 visits. Mean (SD) total payments across all drugs and cost components were $2,477 ($1,842) per visit and $4,966 ($3,841) PPPM, of which IV administration costs were 10.2% of per-visit and 11.4% of PPPM costs, and other drugs and services provided during IV administration were 30.8% of per-visit and 32.2% of PPPM costs. In both the per-visit and PPPM analyses, approximately 80% of costs for other drugs and services (approximately 25% of total treatment costs) were attributed to (a) antihypercalcemic agents (e.g., zoledronic acid: 6%-8% of total treatment cost), (b) colony-stimulating factors (CSFs) (e.g., pegfilgrastim, epoetin: 6%-7%), or (c) other anticancer agents being used off-label or for other conditions (e.g., bevacizumab, irinotecan, carboplatin, vincristine: 11%-12%). The remaining 20% of costs for other drugs and services (approximately 25% of total treatment costs) were attributed to (a) antihypercalcemic agents (e.g., zoledronic acid: 6%-8% of total treatment cost), (b) colony-stimulating factors (CSFs) (e.g., pegfilgrastim, epoetin: 6%-7%), or (c) other anticancer agents being used off-label or for other conditions (e.g., bevacizumab, irinotecan, carboplatin, vincristine: 11%-12%). The remaining 20% of costs for other drugs and services (approximately 25% of total treatment costs) were attributed to (a) antihypercalcemic agents (e.g., zoledronic acid: 6%-8% of total treatment cost), (b) colony-stimulating factors (CSFs) (e.g., pegfilgrastim, epoetin: 6%-7%), or (c) other anticancer agents being used off-label or for other conditions (e.g., bevacizumab, irinotecan, carboplatin, vincristine: 11%-12%).

CONCLUSIONS: For patients being administered a single FDA-approved or NCCN-recommended IV drug for treatment of MBC, IV administration costs accounted for approximately 10%-11% of total cost, and the study drugs accounted for 56%-59%. Other drugs and services accounted for 31%-32%, most of which was attributable to antihypercalcemic agents, CSFs, anticancer drugs being used off-label for breast cancer or for other conditions, and antiemetic agents. Although costs of IV administration are 10%-11% of total IV chemotherapy costs for MBC and would clearly be avoided with the use of oral agents, the extent to which other costs would be avoided or incurred with use of oral agents is unknown and requires further research.

What is already known about this subject

• Breast cancer is the most frequently diagnosed cancer in women and the second most common cause of cancer death in women of all ages in the United States. In 2008, an estimated 250,230 U.S. women will be diagnosed with breast cancer.
• The total annual cost of diagnosing and treating MBC in the United States is an estimated $8.1 billion (in 2004 dollars) for hospital and medical costs, including drug costs and the cost of personnel time and supplies/equipment involved in the preparation, administration, and management of the infused and injectable drugs.
• Limited information exists on the additional costs above the cost of the cancer drug incurred with the administration of IV therapy in patients with MBC. These costs, in addition to the direct drug cost, have been reported to range from 30% across all cancers to 50% in patients with lung cancer.

What this study adds

• Examining 828 patients with MBC with 7,406 visits for treatment with a single IV-administered breast cancer drug over a 41-month time period, the mean total payments across all drugs and cost components were $2,477 per visit and $4,966 PPPM. Costs other than the breast cancer IV drug cost accounted for 41%-43% of total payments, of which 10%-11% was attributable to IV administration and 31%-32% was attributable to other drugs and services.
• Approximately 80% of the costs for other drugs and services (25% of total MBC treatment cost) were attributable to antihypercalcemic agents (e.g., zoledronic acid, pamidronate), CSFs (e.g., pegfilgrastim, filgrastim, epoetin, darbepoetin), and off-label anticancer drugs. Antiemetics (e.g., palonosetron, granisetron) accounted for about 9% of other drugs and services.
In the United States, breast cancer is the most frequently diagnosed cancer in women and ranks second among cancer deaths in women after lung cancer. In 2008, an estimated 250,230 women in the United States will receive a diagnosis of breast cancer—182,460 (72.9%) with invasive/metastatic and 67,770 with in situ cancer—and 40,480 women will die from the disease. An estimated $8.1 billion (in 2004 dollars) in total health care costs is spent annually on the diagnosis and treatment of breast cancer in the United States.

The various options that are available to treat breast cancer can be divided into 2 categories, local treatment or systemic treatment. Local treatment, involving surgery and/or radiation, is directed only at the cancer cells in the breast area. Systemic treatment is the use of medications that travel in the bloodstream to affect or treat cancer cells. Systemic treatments include chemotherapy, hormonal therapy, and targeted therapies (treatments that identify and attack specific cancer cells without harming normal cells) and are often used in combination with surgery or radiation, particularly in early breast cancer.

Systemic treatments may also be used alone in more advanced stages when cancer has metastasized to other parts of the body. In the United States, commonly used chemotherapy agents approved by the U.S. Food and Drug Administration (FDA) for metastatic breast cancer (MBC) include taxanes (docetaxel and paclitaxel), anthracyclines (doxorubicin and epirubicin), gemcitabine, and capecitabine (an oral agent). Commonly used endocrine agents are aromatase inhibitors (anastrozole, letrozole, or exemestane) or estrogen modulators (fulvestrant or tamoxifen). Trastuzumab and lapatinib are newer targeted therapies available for patients with breast cancer with tumors that overexpress ErbB2 (or HER2), a growth factor receptor gene, representing approximately 25%-30% of the patient population with breast cancer. The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 21 leading cancer centers in the United States, develops guidelines for treatment of many types of cancer and may recommend agents that have not received FDA approval. For example, the NCCN treatment guidelines for breast cancer includes vinorelbine as one of several preferred single agents for recurrent or metastatic breast cancer.

Most patients have traditionally been treated with chemotherapy administered intravenously either alone or in combination and, hence, incur additional costs above the drug acquisition cost. These additional costs include the cost of practitioner time for intravenous (IV) administration and other services that may be provided during the clinic visit, ranging from the management of adverse events associated with the administration to the need for additional supportive care agents, specialized equipment, supplies, and other personnel time. Several oral anticancer drugs (e.g., tamoxifen, capecitabine, lapatinib, sorafenib, sunitinib, and dasatinib) have been approved, and numerous others are in development. Use of oral agents may lead to cost savings for payers by avoiding the cost associated with the IV administration and related costs. Other potential advantages of oral cancer therapies include convenience and ease of administration, which are particularly important when patients require treatment over a prolonged period of time because of advances in cancer management.

Most published studies on the economic burden of cancer, including breast cancer, lack sufficient detail to provide a clear understanding of all the cost factors associated with the cancer therapy. One published review of the costs of cancer suggests that costs other than cancer drug costs, such as IV administration procedures, other oral and IV drugs, evaluation and management, laboratory services, and radiology, account for 30% of total costs, whereas a study in lung cancer reports these costs to be around 41%.

The objective of this study was to assess the cost components, from a payer perspective, of providing IV therapy with a single FDA-approved or NCCN-recommended agent to women with MBC in the United States. This study used a novel provider-payer contract database to categorize MBC claims into the following cost components: IV breast cancer therapies, IV administration, and other supportive services. These costs were examined by IV breast cancer drug, payer type, and patient age group.

### Methods

#### Data Source

Data for this study were obtained from the database of Medical Present Value Inc. (MPV), a contract management company located in Austin, Texas (www.mpv.com). MPV maintains a contract and claims management system that supports 46 general/oncology clinics in the United States and contains information on more than 46,000 patients with breast cancer (identified by International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 174.XX, Table 1). The database contains a complete history of diagnoses (ICD-9-CM codes), procedures, and drug therapies received by the patients within the clinics, as well as patient demographics (e.g., age, gender, and geographic region), insurance type (e.g., managed care, indemnity, Medicare, and Medicaid), and insurance product type (e.g., health maintenance organization and preferred provider organization), including third-party payers for private insurance. For every patient clinic visit, MPV maintains the service dates, total charged, and total contracted payments, with individual services, procedures, and drugs broken out by line item (Current Procedural Terminology, Fourth Edition [CPT-4] and Healthcare Common Procedure Coding System [HCPCS] codes).

Treatment costs were estimated using the contracted allowed payment for a claim, not the practice charges, based on adjudication of the claim by the patient’s third-party insurance plan. This contracted payment is defined as the amount that the provider is eligible to receive from all parties, including primary and secondary payers and the patient, based on the contractual agreement with the payer. Because the contracted payment represents the
actual payment to providers from payers, it depicts a more accurate and detailed view of the true economic burden of IV administration to payers than would charges; on average, contracted payments were approximately 51% of provider-submitted charges during the study period.

Based on an Internet search of FDA-approved breast cancer drugs, NCCN clinical practice guidelines, and other sources, 15 drugs were identified (see Appendix) of which 11 therapies were common breast cancer treatments identified and assessed in this study (henceforth referred to as “study drugs”): cyclophosphamide, docetaxel, doxorubicin, fluorouracil, fulvestrant, gemcitabine, non-protein-bound paclitaxel, protein-bound paclitaxel, trastuzumab, vinblastine, and vinorelbine (Table 2). All these drugs are administered intravenously except fulvestrant, which is administered intramuscularly.

Study Cohort

The study cohort consisted of female patients diagnosed with MBC. Patients (a) had 1 or more claims with a diagnosis of breast cancer (ICD-9-CM code 174.XX) and 1 or more claims with a diagnosis of secondary malignant neoplasms of lymph nodes (ICD-9-CM code 196.XX), respiratory and digestive systems (ICD-9-CM code 197.XX), and/or other specified sites (ICD-9-CM code 198.XX) between January 1, 2003, and May 31, 2006 (Table 1); (b) received at least 1 of the 11 single-agent IV breast cancer treatments (Table 2) during a clinic visit; and (c) had a minimum of 1 month follow-up. Diagnoses could be reported in any position on the claim (e.g., primary, secondary, or tertiary.) A total of 46,273 patients with a diagnosis of breast cancer were identified, of whom 8,533 also had a secondary malignant neoplasm diagnosis. Further restricting the sample to patients receiving a single-agent IV breast cancer drug and minimum follow-up of at least 1 month in the dataset resulted in 828 eligible patients (Figure 1). Patient records were restricted to the starting date of the metastatic diagnosis and were followed until either the end date of the study period or the date on which the patient no longer received care at the clinic or died.

This study focuses only on single-agent visits for IV treatment, defined as visits during which patients received a single FDA-approved or NCCN-recommended breast cancer drug. This decision was made for several reasons. First, single-agent visits comprised a majority (73%) of the IV visits in the data. Second, if visits in which multiple therapies were administered had been used as the unit of analysis, the number of visits for the various unique combination therapies would have been significantly smaller, limiting the interpretability of the results. For example, 18 of the 33 combination therapies identified in the data would have contributed 10 or fewer visits to the dataset, compared with an average of 673 visits for single-agent breast cancer therapy (7,406 total visits divided by 11 breast cancer agents). Third, previous research has shown that costs incurred in addition to breast cancer drug costs are higher for combination therapy than for monotherapy. For example, costs associated with the administration of trastuzumab-based combination therapies were estimated in 1 study to be about 30.3% of total costs (10.9% for IV administration and 19.4% for other visit-related services and drugs provided during IV administration), whereas costs associated with administration of trastuzumab alone were 21.8% of total costs (8.5% for IV administration and 13.3% for other

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TABLE 1  ICD-9-CM Codes Used to Identify the Study Cohort

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>174.0</td>
<td>Nipple and areola</td>
</tr>
<tr>
<td>174.1</td>
<td>Central portion</td>
</tr>
<tr>
<td>174.2</td>
<td>Upper-inner quadrant</td>
</tr>
<tr>
<td>174.3</td>
<td>Lower-inner quadrant</td>
</tr>
<tr>
<td>174.4</td>
<td>Upper-outer quadrant</td>
</tr>
<tr>
<td>174.5</td>
<td>Lower-outer quadrant</td>
</tr>
<tr>
<td>174.6</td>
<td>Axillary tail</td>
</tr>
<tr>
<td>174.8</td>
<td>Other specified sites of female breast</td>
</tr>
<tr>
<td>174.9</td>
<td>Breast (female), unspecified</td>
</tr>
<tr>
<td>196.0</td>
<td>Lymph nodes of head, face, and neck</td>
</tr>
<tr>
<td>196.1</td>
<td>Intrathoracic lymph nodes</td>
</tr>
<tr>
<td>196.2</td>
<td>Intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>196.3</td>
<td>Lymph nodes of axilla and upper limb</td>
</tr>
<tr>
<td>196.5</td>
<td>Lymph nodes of inguinal region and lower limb</td>
</tr>
<tr>
<td>196.6</td>
<td>Intrapelvic lymph nodes</td>
</tr>
<tr>
<td>196.8</td>
<td>Lymph nodes of multiple sites</td>
</tr>
<tr>
<td>196.9</td>
<td>Site unspecified</td>
</tr>
<tr>
<td>197.0</td>
<td>Lung</td>
</tr>
<tr>
<td>197.1</td>
<td>Mediastinum</td>
</tr>
<tr>
<td>197.2</td>
<td>Pleura</td>
</tr>
<tr>
<td>197.3</td>
<td>Other respiratory organs</td>
</tr>
<tr>
<td>197.4</td>
<td>Small intestine, including duodenum</td>
</tr>
<tr>
<td>197.5</td>
<td>Large intestine and rectum</td>
</tr>
<tr>
<td>197.6</td>
<td>Retropertioneum and peritoneum</td>
</tr>
<tr>
<td>197.7</td>
<td>Liver, specified as secondary</td>
</tr>
<tr>
<td>197.8</td>
<td>Other digestive organs and spleen</td>
</tr>
<tr>
<td>198.0</td>
<td>Kidney</td>
</tr>
<tr>
<td>198.1</td>
<td>Other urinary organs</td>
</tr>
<tr>
<td>198.2</td>
<td>Skin</td>
</tr>
<tr>
<td>198.3</td>
<td>Brain and spinal cord</td>
</tr>
<tr>
<td>198.4</td>
<td>Other parts of nervous system</td>
</tr>
<tr>
<td>198.5</td>
<td>Bone and bone marrow</td>
</tr>
<tr>
<td>198.6</td>
<td>Ovary</td>
</tr>
<tr>
<td>198.7</td>
<td>Adrenal gland</td>
</tr>
<tr>
<td>198.8</td>
<td>Other specified sites</td>
</tr>
</tbody>
</table>

visit-related services and drugs provided during IV administration). To address the concern of potential bias by focusing on monotherapy, a sensitivity analysis was performed to compare the primary cost categories of monotherapy with the 27% of visits where 2 or more (combination) approved or recommended breast cancer therapies were administered.

Although patients receiving more than 1 FDA-approved or NCCN-recommended regimen were excluded from the study sample, patients receiving an FDA-approved or NCCN-recommended agent coupled with an off-label agent were retained for analysis. This decision was made because off-label use of anticancer agents is prevalent in cancer treatment. A total of 170 (20.5%) patients were using both an FDA-approved or NCCN-recommended treatment and at least 1 off-label anticancer treatment.

Outcome Measures and Analysis

Costs were calculated using 2 approaches: average cost per IV administration visit and average cost per patient per month (PPPM). IV administration visits were selected based on administration of an IV therapy during a clinic visit and identified by the claim ID and date. All services, materials, and drugs identified by the claim line items during these visits were used in the IV therapy administration visit cost analysis. To calculate PPPM costs, therapy duration in months for each patient was calculated using IV study drug start and end dates. Start dates were determined using the filing date of the appropriate J-code claim (Table 2) following a 30-day washout period (i.e., no study drug IV therapy prescribed in prior 30 days). End dates were determined by a 30-day washout period following the last IV therapy claim for a study drug or the end of the study period. Patients could have stopped IV therapy for several reasons, including discontinuation of the therapy, switching to another monotherapy or combination therapy, receiving care in a hospital or another treatment facility, or death. The line items from the visits identified in the IV visit analysis were then aggregated into therapy months based on therapy duration and reported on a PPPM basis.

It is important to note that some of the monotherapy visits were excluded in the PPPM analysis. This pattern occurred when the monotherapy visits of a patient obtaining different drugs overlapped one another. Although these patients could be included in the monotherapy visit analysis because they were receiving only 1 IV breast cancer study drug during each visit, the PPPM calculation would involve combining multiple study drug therapies within the same patient-month. For example, if a patient received drug A for 2 months and then drug B for 2 months, all these visits would be included in both the monotherapy and PPPM analyses. However, if a patient received drug A in months 1-4 and received drug B in months 3 and 4, all these visits would be included in the IV visit analysis since they were single-agent visits, but only drug A for months 1 and 2 would be included in the PPPM analysis because the patient was receiving combination therapy from a duration viewpoint during months 3 and 4. To maintain the

### Table 2: Breast Cancer Drugs and HCPCS Codes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Common Brand Name(s)</th>
<th>HCPCS Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-bound paclitaxel</td>
<td>Abraxane</td>
<td>J9264</td>
</tr>
<tr>
<td>Doxorubicin b</td>
<td>Adriamycin, Rubex</td>
<td>J9000-J9001</td>
</tr>
<tr>
<td>Fluorouracil b</td>
<td>Adrucil</td>
<td>J9190</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Taxotere</td>
<td>J9170</td>
</tr>
<tr>
<td>Non-protein-bound paclitaxel</td>
<td>Taxol</td>
<td>J9265</td>
</tr>
<tr>
<td>Vinblastine b</td>
<td>Vinblastine</td>
<td>J9360</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>J9355</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Gemzar</td>
<td>J9201</td>
</tr>
<tr>
<td>Fulvestrant (IM)</td>
<td>Faslodex</td>
<td>J9395</td>
</tr>
<tr>
<td>Cyclophosphamide b</td>
<td>Cytoxan, Neosar</td>
<td>J9070, J9080, and J9090-J9097</td>
</tr>
<tr>
<td>Vinorelbine b</td>
<td>Navelbine</td>
<td>J9390</td>
</tr>
</tbody>
</table>

a Two additional drugs—epirubicin and thiopeta—met study criteria for inclusion but are not shown in the table because no patients in the study cohort received them.

b Available generically.

HCPCS = Health Care Procedure Coding System; IM = intramuscular.

### FIGURE 1

Selection of Patients with Metastatic Breast Cancer Receiving IV Monotherapy a

- Patients with a breast cancer diagnosis from January 1, 2003 to May 31, 2006
  - N=46,273

- Patients with a secondary malignant neoplasm diagnosis
  - N=8,533 (18.4%)

- Patients with monotherapy or combination therapy IV administration visit
  - N=999 (11.7%)

- Patients with monotherapy IV administration visits only
  - N=828 (82.9%)

a An unknown number of the 8,533 patients with metastatic breast cancer were either treated at other oncology clinics or not treated at all. IV=intravenous.
consistency of examining monotherapy across both measures, the PPPM analysis was restricted to therapy durations where patients received only 1 therapy.

We categorized the various billable components into 1 of 3 cost categories: (1) IV breast cancer study drug; (2) administration of all IV medications, including the breast cancer study drug; and (3) other visit-related services and drugs. The IV administration category included all codes and costs associated with the duration of administration (e.g., CPT code 96413 covers chemotherapy administration via intravenous infusion technique up to 1 hour for a single or initial drug). The last category, other visit-related services and drugs, was divided further into 4 categories: (3a) other injectable drugs (e.g., antianemia drugs epoetin and darbepoetin) and concomitant oral drugs (e.g., diphenhydramine, granisetron, and ondansetron), (3b) evaluation and management services, (3c) supplies and equipment, and (3d) miscellaneous administration-related services. Concomitant oral drugs are those which are administered as an initial dose as supportive care at the time of chemotherapy treatment and are billed during that visit. To provide additional detail on the other injectable drugs and concomitant oral drugs administered during these visits, we divided this category into 11 drug categories: antihypercalcemic drugs, colony-stimulating factors (CSFs), anticancer agents (used in an off-label indication or for other conditions), antiemetic agents, saline solution, corticosteroids, heparin, antihistamines, histamine-2 (H2) antagonists, iron, and miscellaneous/unclassified agents. For patients using both a study drug and 1 or more off-label anticancer agents, costs for the off-label drug were placed into the “other visit-related services” category (c-1).

For each of the 3 major cost components—IV study drug, IV administration, and other visit-related costs—drug, payer type, and patient age groups were compared using the Kruskal-Wallis test, a nonparametric one-way analysis of variance.

Results

Study Cohort Characteristics

A total of 828 eligible patients with 7,406 visits for IV therapy for any of the 11 study drugs were identified. Demographic characteristics are presented in Table 3. More than three-quarters (76.7%) of the patients were younger than 65 years of age. Geographically, the patients were more representative of the southern and western United States than of other regions, and few patients were from the northeastern United States. The majority (about 65%) of patients had private insurance (i.e., employer-based, managed care, or indemnity health insurance); 23.4% had Medicare, 3.3% Medicaid, and 8.1% other or unknown insurance type.

Overall Payments for Patients With MBC

Payment amounts overall and by cost category for the per-visit and PPPM analyses are presented in Table 4. The mean (SD) total payments across all drugs and cost categories were $2,477 ($1,842) per visit and $4,966 ($3,841) PPPM. In the per-visit analysis, IV breast cancer drug mean payment amount accounted for 59.0% ($1,463) of the total, with IV administration responsible for 10.2% ($252) and other services provided at the visit accounting for the remaining 30.8% ($763). The PPPM analysis exhibited a breakdown similar to that of the per-visit analysis: $2,800 (36.4%) for IV cancer drug, $568 (11.4%) for IV administration, and $1,598 (32.2%) for other visit-related services and drugs. In both analyses, 99% of costs for the category “other services provided at visit” were attributable to drug costs for other injectable drugs and concomitant oral drugs.

The antihypercalcemic/bone resorption agents such as zoledronic acid and pamidronate comprised the highest-cost drug category in the visit analysis, accounting for 24.7% ($188 per visit) of the cost of other visit-related services, followed by CSFs such as pegfilgrastim, filgrastim, epoetin, and darbepoetin, which accounted for another 20.2% ($154 per visit) of the category. An additional $273 per visit (35.8%) of the other visit-related services cost was attributable to anticancer drugs that may be used off-label or to treat other conditions, including antineoplastic agents (e.g., bevacizumab), platinum agents (e.g., carboplatin), and chemotherapeutic agents (e.g., vincristine).

Other drugs with high prevalence included the supportive care antiemetics (e.g., palonosetron, granisetron; $65.97 per
The remaining other visit-related costs were supplies and equipment provided during the IV administration visit. The most frequently billed procedures in the evaluation and management services category were physician assessments for chemotherapy administration or side-effects related to chemotherapy, including nausea and/or vomiting, fatigue, and pain ($4.31 per visit). During these visits, the most common supplies and equipment used were IV needles, sterile water, dressing pads, and infusion supplies ($1.87 per visit). Finally, the miscellaneous administration-related services category primarily included fluid collection and laboratories such as metabolic panels and red and white blood cell counts ($2.24 per visit). A similar pattern for these cost categories was observed in the PPPM analysis.

**Payments by IV Cancer Drug**

Payments in total and for each of the 11 breast cancer drugs (including intramuscular [IM] fulvestrant) and 3 cost categories, by visit and PPPM, are presented in Table 5. Among the 828 patients, the most commonly used drugs included non-protein-bound paclitaxel (31.5% of patients) and trastuzumab (25.6%), whereas the least commonly used drugs included protein-bound paclitaxel (2.3%) and cyclophosphamide (2.1%).

Average total contracted payments significantly differed by drug in the per-visit (P<0.001) and PPPM (P<0.001) analyses. The highest total payments per visit were observed for protein-bound paclitaxel ($4,347) and doxorubicin ($3,145). The lowest total payments were observed for vinorelbine ($1,270) and cyclophosphamide ($1,532). In the PPPM cost analysis, protein-bound paclitaxel and fluorouracil had the highest average total PPPM costs ($12,441 and $6,920, respectively), whereas IM fulvestrant and cyclophosphamide had the lowest average total costs ($2,560 and $1,751, respectively). Examining IV breast cancer drug costs alone, the most expensive treatments per visit and PPPM were protein-bound paclitaxel, docetaxel, and trastuzumab, whereas fluorouracil and cyclophosphamide were the least expensive.
Overall Costs Per Patient With Metastatic Breast Cancer (N = 828) by Visit and Month

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Overall Costs Per Patient With Metastatic Breast Cancer (N=828) by Visit and Month (continued from previous page)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPPM</td>
<td>No. of Therapy-Months</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Total</td>
<td>3646</td>
</tr>
<tr>
<td>1. IV study drug</td>
<td></td>
</tr>
<tr>
<td>2. IV administration (all drugs)</td>
<td></td>
</tr>
<tr>
<td>3. Other visit-related services and drugs</td>
<td></td>
</tr>
<tr>
<td>3a. Other injectable drugs and concomitant oral drugs(^a)</td>
<td></td>
</tr>
<tr>
<td>- Antineoplastic agents (e.g., bevacizumab)(^b)</td>
<td></td>
</tr>
<tr>
<td>- Colonystimulating factors (e.g., pegfilgrastim, filgrastim, epoetin, darbepoetin)</td>
<td></td>
</tr>
<tr>
<td>- Antineoplastic agents (e.g., zoledronic acid)</td>
<td></td>
</tr>
<tr>
<td>- Platinum agents (e.g., carboplatin, oxaliplatin)(^b)</td>
<td></td>
</tr>
<tr>
<td>- Chemotherapeutic agents (e.g., irinotecan, vincristine)(^b)</td>
<td></td>
</tr>
<tr>
<td>- Antiemetic agents (e.g., palonosetron, granisetron)</td>
<td></td>
</tr>
<tr>
<td>- Saline solution, dextrose water</td>
<td></td>
</tr>
<tr>
<td>- Corticosteroids (e.g., dexamethasone)</td>
<td></td>
</tr>
<tr>
<td>- Heparin</td>
<td></td>
</tr>
<tr>
<td>- Antihistamine (e.g., diphenhydramine)</td>
<td></td>
</tr>
<tr>
<td>- Histamine-2 receptor antagonists (e.g., ranitidine)</td>
<td></td>
</tr>
<tr>
<td>- Iron</td>
<td></td>
</tr>
<tr>
<td>- Miscellaneous/unclassified agents</td>
<td></td>
</tr>
<tr>
<td>3b. Office visit: evaluation and management services(^c)</td>
<td></td>
</tr>
<tr>
<td>3c. Supplies and equipment(^d)</td>
<td></td>
</tr>
<tr>
<td>3d. Miscellaneous administration-related services(^e)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Includes other injectable drugs administered and oral drugs administered as an initial dose for supportive care at the time of chemotherapy treatment during the breast cancer IV administration visit.

\(^b\) Breast cancer chemotherapy therapy was restricted to FDA-approved or National Comprehensive Cancer Network guideline-recommended agents. These anticancer agents were not indicated for breast cancer during study period.

\(^c\) Primarily includes physician assessments for chemotherapy administration or side effects related to chemotherapy including nausea and/or vomiting, fatigue, and pain; these codes include G9021-G9024 (chemotherapy assessment for nausea and vomiting) and G9029-G9032 (chemotherapy assessment for lack of energy [fatigue]). Side effects related to chemotherapy accounted for about 60% of total costs in this category.

\(^d\) Includes non-coring needles, sterile water, dressing pads, and infusion supplies.

\(^e\) Includes fluid collection and laboratories such as blood collection by venipuncture, metabolic panels, red and white blood cell count, and lactate dehydrogenase.

3 Patients receiving administrations of 2 or more different drugs at separate visits during the same month were included in the per-visit analysis (monotherapy during visit).

Although IV breast cancer drug cost variation was expected, we observed that the costs associated with administration and with other visit-related services and drugs also varied significantly between agents (P<0.001). Costs associated with IV administration ranged from $110 to $490 per visit across drugs, representing 6.3% to 21.3% of total costs, and from $114 to $1,037 PPPM across drugs, representing 6.5% to 33.7% of total costs. Costs associated with other visit-related services and drugs also varied significantly across therapies (P<0.001), showing greater variation than did costs associated with IV administration. These costs varied from $336 to $2,573 per visit and $602 to $5,164 PPPM across drugs. These costs as a percentage of total costs ranged from 13.3% (trastuzumab) to 85.9% (vinblastine) on a per-visit basis and from 13.5% (trastuzumab) to 74.6% (fluorouracil) on a PPPM basis.

Payment by Payer Type and Patient Age

Significant differences in costs for study drug, IV administration, and other visit-related services and drugs were observed across payer types in both the per-visit (P<0.001) and PPPM (P<0.001) analyses (Figure 2). The overall mean payment per visit (PPPM) was $2,924 ($6,092) for managed care; $2,672 ($5,192) for indemnity; $1,582 ($3,007) for Medicare; $1,594 ($3,565) for...
### Table 5: Costs by Drug Per Patient With Metastatic Breast Cancer—Per Visit and Per Month

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients (n)</th>
<th>Visits (n)</th>
<th>Total Mean Costs ($)</th>
<th>Study Drug Mean Costs ($)</th>
<th>IV Administration Mean Costs ($)</th>
<th>Other Visit-Related Services Mean Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per Visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Study Drugs</td>
<td>828</td>
<td>7406</td>
<td>2,477.32</td>
<td>1,462.80</td>
<td>251.74</td>
<td>762.78</td>
</tr>
<tr>
<td>Protein-bound paclitaxel</td>
<td>19</td>
<td>94</td>
<td>4,346.72</td>
<td>3,044.46</td>
<td>361.29</td>
<td>940.97</td>
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<tr>
<td>Doxorubicin</td>
<td>72</td>
<td>288</td>
<td>3,145.11</td>
<td>1,944.22</td>
<td>274.99</td>
<td>825.90</td>
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<tr>
<td>Fluorouracil</td>
<td>28</td>
<td>186</td>
<td>3,100.79</td>
<td>32.10</td>
<td>495.57</td>
<td>16.0</td>
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<tr>
<td>Docetaxel</td>
<td>151</td>
<td>761</td>
<td>3,042.66</td>
<td>2,080.27</td>
<td>204.88</td>
<td>6.7</td>
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<tr>
<td>Non-protein-bound paclitaxel</td>
<td>261</td>
<td>1450</td>
<td>2,803.64</td>
<td>1,213.84</td>
<td>352.97</td>
<td>12.6</td>
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<tr>
<td>Vinblastine</td>
<td>1</td>
<td>2</td>
<td>2,620.60</td>
<td>205.20</td>
<td>164.50</td>
<td>6.3</td>
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<tr>
<td>Trastuzumab</td>
<td>212</td>
<td>2416</td>
<td>2,526.41</td>
<td>1,976.27</td>
<td>213.66</td>
<td>8.5</td>
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<tr>
<td>Gemcitabine</td>
<td>137</td>
<td>973</td>
<td>2,249.60</td>
<td>1,116.12</td>
<td>289.11</td>
<td>12.9</td>
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<tr>
<td>Fulvestrant</td>
<td>119</td>
<td>517</td>
<td>1,660.29</td>
<td>917.49</td>
<td>110.37</td>
<td>6.6</td>
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<tr>
<td>Cyclophosphamide</td>
<td>17</td>
<td>21</td>
<td>1,531.68</td>
<td>94.33</td>
<td>326.17</td>
<td>21.3</td>
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<tr>
<td>Vinorelbine</td>
<td>103</td>
<td>698</td>
<td>1,270.38</td>
<td>431.03</td>
<td>185.71</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
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<td></td>
<td></td>
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<tr>
<td><strong>PPPM</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Study Drugs</td>
<td>776</td>
<td>3646</td>
<td>4,965.97</td>
<td>2,200.31</td>
<td>567.80</td>
<td>1,597.87</td>
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<tr>
<td>Protein-bound paclitaxel</td>
<td>37</td>
<td>34</td>
<td>12,441.07</td>
<td>8,205.76</td>
<td>1,057.13</td>
<td>3,178.17</td>
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<tr>
<td>Fluorouracil</td>
<td>27</td>
<td>89</td>
<td>6,919.59</td>
<td>3,850.62</td>
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<td>3,163.70</td>
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<tr>
<td>Non-protein-bound paclitaxel</td>
<td>241</td>
<td>679</td>
<td>6,323.25</td>
<td>2,994.86</td>
<td>856.41</td>
<td>13.5</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>174</td>
<td>1040</td>
<td>5,256.34</td>
<td>2,454.46</td>
<td>856.41</td>
<td>13.5</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>137</td>
<td>426</td>
<td>5,090.27</td>
<td>2,594.41</td>
<td>659.72</td>
<td>14.1</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>117</td>
<td>378</td>
<td>4,883.22</td>
<td>2,556.41</td>
<td>687.92</td>
<td>14.1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>66</td>
<td>258</td>
<td>3,734.32</td>
<td>1,924.88</td>
<td>372.25</td>
<td>10.0</td>
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<tr>
<td>Vinorelbine</td>
<td>87</td>
<td>234</td>
<td>3,712.88</td>
<td>2,247.73</td>
<td>381.98</td>
<td>15.7</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>10</td>
<td>11</td>
<td>2,559.83</td>
<td>1,127.83</td>
<td>683.74</td>
<td>33.7</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>109</td>
<td>497</td>
<td>1,750.87</td>
<td>1,035.05</td>
<td>113.55</td>
<td>6.5</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Includes other injectable drugs and concomitant oral drugs (e.g., antihypercalcemic agents, colony-stimulating factors, anticancer agents, and antiemetic agents), evaluation and management services, supplies and equipment, and miscellaneous administration-related services.

*a Comparisons by study drug on costs for study drug, IV administration, and other services were statistically significant in both the IV-visit analysis (P < 0.001) and the PPPM analysis (P < 0.001) using a Kruskal-Wallis test. Vinblastine was excluded due to low number of visits. Pairwise comparisons were performed using Dunn's nonparametric multiple comparison test.

Numbers in cells do not sum to total because some patients used more than 1 drug during the study period.

**Statistical Test Results for Per-Visit Pairwise Comparisons:** Cost of study drug — All pairwise comparisons were significant at P < 0.05 except for cyclophosphamide vs. fluorouracil, cyclophosphamide vs. vinorelbine, and gemcitabine vs. non-protein-bound paclitaxel. Administrative costs — All pairwise comparisons were significant at P < 0.05 except for protein-bound paclitaxel vs. cyclophosphamide, protein-bound paclitaxel vs. fluorouracil, protein-bound paclitaxel vs. non-protein-bound paclitaxel, cyclophosphamide vs. docetaxel, cyclophosphamide vs. doxorubicin, cyclophosphamide vs. fluorouracil, cyclophosphamide vs. gemcitabine, cyclophosphamide vs. non-protein-bound paclitaxel, cyclophosphamide vs. vinorelbine, docetaxel vs. vinorelbine, docetaxel vs. trastuzumab, docetaxel vs. vinorelbine, and doxorubicin vs. gemcitabine. Other visit-related services — All pairwise comparisons significant at P < 0.05 except for protein-bound paclitaxel vs. cyclophosphamide, protein-bound paclitaxel vs. docetaxel, protein-bound paclitaxel vs. doxorubicin, protein-bound paclitaxel vs. fluorouracil, protein-bound paclitaxel vs. fulvestrant, protein-bound paclitaxel vs. trastuzumab, protein-bound paclitaxel vs. vinorelbine, cyclophosphamide vs. docetaxel, cyclophosphamide vs. doxorubicin, cyclophosphamide vs. fluorouracil, cyclophosphamide vs. gemcitabine, cyclophosphamide vs. non-protein-bound paclitaxel, cyclophosphamide vs. vinorelbine, docetaxel vs. vinorelbine, doxorubicin vs. gemcitabine, doxorubicin vs. vinorelbine, and gemcitabine vs. non-protein-bound paclitaxel. IV=intravenous; MBC=metastatic breast cancer; PPPM=per patient per month.
Medicaid; and $1,646 ($3,476) for the other/unknown category of patients. When comparing the additional costs beyond the breast cancer study drug as a percentage of total payments, Medicaid had the lowest cost of IV administration visit at $77 per visit (4.9% of total costs) and $160 PPPM (4.5% of total costs), whereas managed care patients had the highest cost of IV administration at $310 per visit (10.6% of total costs) and $718 PPPM (11.8% of total costs). Similar to IV administration costs, Medicaid patients had the lowest cost of other visit-related services and drugs at $318 per visit (19.9% of total costs) and $586 PPPM (16.4% of total costs). However, patients covered by indemnity insurance had the highest costs for other visit-related services and drugs at $1,015 per visit (38.0% of total costs) and $2,075 PPPM (40.0% of total costs).

There were also significant differences in payments to providers by patient age group for study drug, IV administration, and other visit-related services and drugs in both the per-visit (P<0.001) and PPPM (P<0.001) analyses (Figure 3). Patients aged 65 years or older (Medicare-eligible patients) had the lowest average total costs per visit and PPPM, reflecting the lower payments by Medicare. In contrast to the analysis by payer type, little age-related variation was observed for costs associated with IV administration and other visit-related services and drugs, which ranged, respectively, from 10%-12% and 27%-33% of
In the sensitivity analysis limited to patients taking 2 or more study drugs (combination therapy), results were similar to those observed for the monotherapy patients. Costs for IV administration and other visit-related costs were 38.3% of total cost per visit (detailed data not shown), compared with 41.0% for monotherapies.

Discussion
The objective of this study was to evaluate the costs associated with the administration of single-agent IV therapies in patients with MBC. To estimate the cost components, we examined more than 800 patients with MBC with more than 7,400 clinic visits from a large, national practice management system. Costs were analyzed on a per-visit and PPPM basis. The results showed average contracted payments of $2,477 per visit and $4,966 PPPM, with IV administration accounting for 10%-11% of the total and costs for other visit-related drugs, including antihypercalcemic agents, CSFs, and anticancer drugs being used off-label or for other conditions, accounting for 31%-32% of the total cost.

These costs above the drug acquisition cost for the principal chemotherapy drug represent a significant economic burden to payers. Even though this study focused on MBC, these IV administration and other visit-related costs have also been reported to comprise a significant portion of total costs for early stage breast cancer. Results of the present study are comparable to those of a previous study based on administrative claims data for lung cancer, which reported non-lung cancer drug costs associated with...
IV administration and related services to be 50% and 41% of total payments per visit, for small cell lung cancer and all types of lung cancer, respectively.15

In assessing the payment breakdown based on individual IV cancer drug, variability was observed for costs associated with administration and more so for the costs associated with other visit-related services and drugs. Part of the variation in these costs can be explained by the lower drug costs of the generic breast cancer therapies. For example, mean total costs per visit for generic fluorouracil treatment were $3,101, of which drug costs were only $32 (1.0%), costs for IV administration were $496 (16.0%), and costs for other visit-related services and drugs were $2,573 (83.0%). In contrast, the corresponding total cost ($4,347) breakdown for branded protein-bound paclitaxel was $3,044 (70.0%) for the study drug, $361 (8.3%) for IV administration, and $941 (21.6%) for other services. For example, to avoid the occurrence of severe hypersensitivity reactions, patients receiving non-protein-bound paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine, and H2-blockers such as ranitidine or cimetidine; however, the cost for these agents is low—$4.51 per visit for corticosteroids, $0.47 per visit for antihistamines, and $0.39 per visit for H2-blockers.

It is also possible that the older agents may have been combined with newer, nonapproved, and nonrecommended anticancer agents. For example, bevacizumab was neither FDA-approved nor NCCN-recommended as a single agent for breast cancer for the study period, and may have been used more frequently in combination with older drugs (e.g., fluorouracil); this treatment pattern would result in high costs for the “other visit-related services and drugs” category.

Contracted allowed payments were also found to vary considerably by payer type. As expected, patients enrolled in government-funded programs (Medicaid and Medicare) had lower overall payments than did managed care and indemnity insured patients. This difference is probably attributable to differences in reimbursement rates for administration of IV therapies between government-funded and private insurance. Additionally, the analysis showed that Medicaid patients incurred less than 25% of total payments for additional costs above breast cancer study drug costs, whereas managed care and indemnity insured patients incurred more than 40% of total payments for these costs. However, the percentage of costs other than breast cancer study drug costs as a percentage of total costs was similar (40% per visit and 44% PPPM) in both Medicare and managed care. The patient age group analysis showed that, as in the payer type analysis, patients with MBC aged 65 years and older (i.e., Medicare eligible) had the lowest overall payments. Few differences in costs among the remaining age groups were observed.

Although this study does not compare the total costs of oral therapies with those of IV therapies for metastatic breast cancer, the increasing availability and use of effective oral therapies might help provide cost offsets in the treatment of MBC. The costs specifically associated with administration of the IV therapy are substantial and would clearly be avoided with the use of oral agents. Some of the other costs associated with the drugs and services provided at the time of IV administration (e.g., drugs used to dilute or reconstitute the IV product or to manage side effects associated with a particular IV therapy) may possibly be avoided with the use of oral agents. Even if an all-IV combination therapy is partially replaced with an oral therapy (i.e., IV plus IV replaced by IV plus oral), some of the costs associated with IV administration (depends upon length of time required to administer 2 or more IV therapies) might be avoided. However, the extent of cost avoidance for services other than IV administration is unknown and was not measured by this study. We also did not assess the possibility of any added costs associated with oral agents such as noncompliance or treatment of possible side effects with oral agents (e.g., gastrointestinal side effects).

Research evidence about costs of treatment with IV-administered versus oral chemotherapeutic drugs is limited. A recent non-peer-reviewed study delivered in a poster presentation by Giuliani et al. evaluated the economic impact of treatment with (a) oral capecitabine plus IV cisplatin versus (b) IV fluorouracil plus IV cisplatin among patients with advanced gastric cancer in an Italian clinic.18 The costs of the 2 regimens were estimated based on trial data on actual dose and the number of administrations. The adverse event profiles were used to estimate the costs of treating these events. Indirect costs for time and travel for study drug administration were estimated. The oral plus IV regimen received 5.2 cycles of therapy versus 4.6 cycles in the all IV regimen. The oral capecitabine-containing regimen had 17.6 fewer hospital outpatient clinic visits than did the IV fluorouracil-containing regimen; the difference yielded a net cost saving of approximately $2,686 per patient, but no statistical tests were reported. Additionally, due to the additional 17.6 visits for infusion of fluorouracil, patients incurred substantially greater indirect costs in terms of lost time and travel expenses. In a randomized multicenter study of patients with small cell lung cancer, Pashko et al. compared (a) IV etoposide plus IV cisplatin (n = 41) versus (b) oral etoposide plus IV cisplatin (n = 42) and reported a cost savings of 17% ($2,002 for the IV versus $1,653 for the oral regimen, a difference of $349) for the patients receiving the oral plus IV regimen but did not report the results of statistical tests.19

As demonstrated by Giuliani et al., in addition to the possible direct cost savings of oral chemotherapeutic drugs, there may be additional benefits from a patient perspective in terms of time and indirect cost savings resulting from fewer clinic visits for IV administration.18 Several studies have demonstrated patient preferences for oral over IV cancer therapies, provided that efficacy is not compromised by receiving an oral agent.20-22 Fallowfield et al.20 found greater preference for daily tablets of
endocrine therapy over monthly IM injections among women with breast cancer. The major reasons for preference of oral therapy included convenience and dislike for needles, although almost 49% of patients indicated that they sometimes forgot and about 13% opted not to take their medication at certain times. In a study by Liu et al., 103 patients with cancer were asked about their preference for oral or IV chemotherapy. Patients were told initially that frequency of laboratory evaluations and clinic visits to see a doctor and risks of toxicities of oral or intravenous regimens were comparable. Almost 90% of patients expressed a preference for oral chemotherapy. The predominant reason for this result appeared to be problems with IV access (pain and difficulty starting an IV line) or convenience of administration outside a clinic setting. Gornas et al. reported in a poster presentation the results of a survey of 218 female patients with MBC who were eligible for oral capecitabine; patients were asked about factors that influenced their preference for oral therapy. The most common reason for choosing oral capecitabine, cited by 71% of patients, was its more convenient form of drug delivery. Other reasons given included a preference to receive drugs in a “more friendly way” and to stay at home during therapy. However, unlike injectable drugs that are covered under the medical benefit, oral drugs typically would be covered under the pharmacy benefit—hence, any impact on patient out-of-pocket expenses would need to be weighed against these patient benefits.

Limitations
First, we excluded combination drug regimens from this analysis. However, this method excluded only 13% of patients with MBC and 27% of IV visits recorded in the database for the study period. A sensitivity analysis examining costs for the combination therapy visits showed results that were similar to those of the study analyses for monotherapy patients, including cost percentages across breast cancer IV therapy, IV administration, and other drugs and visit-related costs. Focusing on monotherapy regimens permitted us to capture a majority of the IV visits and report the cost components by therapy.

Second, we observed IV breast cancer treatment for only 11.7% of the patients with MBC. Some of these patients with MBC were referred to facilities that were not captured in the data. Third, the accuracy of diagnostic coding of breast cancer and metastasis, and other coding or administrative errors, may have affected the validity of the cost estimates. For example, some patients with MBC may have not received a secondary metastatic ICD-9-CM code and thus were not included in this study. Fourth, given the limited time frame of the study, it is possible that the patients' entire history of IV breast cancer therapy may not have been captured. However, this potential limitation has been addressed by using methods that are not reliant on complete patient therapy histories but based on estimating costs per IV administration visit or cost per month, which are less prone to loss-to-follow-up problems.

Fifth, because health care services delivered at non-IV administration visits were excluded in this study, it is possible that other medical costs not measured in claims for the day of IV administration differ between patients on alternative therapies or insurance types. For example, if a patient returned to the facility at a later date for issues related to the IV therapy but an IV study drug was not administered during this visit, these costs would not be captured. Furthermore, due to the nature of administrative data (we did not have access to patient medical records), only minimal patient information was available. We were not able to examine the impact of clinical (e.g., disease severity and comorbidities) and nonclinical factors (e.g., formulary status of drugs) on costs across therapies. Also, although we were able to measure the total amount that the provider is eligible to receive from both payers and the patient from out-of-pocket payments, we were unable to determine what portion of this aggregated payment was paid by the patient.

Finally, although costs of IV administration are substantial and would clearly be avoided with the use of oral agents, we did not directly compare total costs for treatment using oral versus IV chemotherapeutic agents. We also did not assess the possibility of added costs associated with oral agents, such as noncompliance or treatment for gastrointestinal or other side effects.

Conclusions
Among patients with MBC treated with an IV-administered breast cancer drug, IV breast cancer drugs accounted for 56%-59% of total cost, IV administration costs accounted for 10%-11% of total costs, and 31%-32% of total costs were attributable to other drugs and services, primarily antihypercalcemic agents, CSFs, and anticancer drugs being used off-label or for other conditions. The use of safe and effective oral breast cancer therapies could potentially offset some of the costs of treating patients with MBC by reducing personnel time, clinic visits, and supplies and equipment associated with IV administration. Future research should include a direct comparison of oral versus IV drug costs in order to investigate these potential implications as well as to gain an understanding of both the costs and clinical implications of oral versus IV therapies when administered as sequential or combination therapy.
Analysis of Costs Associated With Administration of Intravenous Single-Drug Therapies in Metastatic Breast Cancer in a U.S. Population

Authors

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DISCLOSURES

Funding for this study was provided by GlaxoSmithKline. Amonkar and Smith are employees of GlaxoSmithKline, and Stavarakas reported previous service as a consultant to GlaxoSmithKline. Skonieczny is employed by Medical Present Value Inc., which provides services to medical groups, including methods to maximize revenue. All authors contributed to the concept and study design. Skonieczny collected the data, with assistance from Stavarakas. The data were interpreted primarily by Kruse and Amonkar. The manuscript was written primarily by Kruse, Amonkar, and Smith. Kruse, Amonkar, and Smith made the largest contribution to manuscript revision.

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## APPENDIX

### Supplemental Information on Study Drug Selection

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved for Breast Cancer</th>
<th>Listed as Preferred Single IV Chemotherapeutic Agent for MBC in NCCN Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-bound paclitaxel</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Yes</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-protein-bound paclitaxel</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Yes</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Yes</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fulvestrant (IM)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Epirubicin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thiotepa&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bleomycin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mitoxantrone&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup> These 15 drugs were identified in the initial search of single-agent breast cancer drugs using a combination of sources, including the FDA Web site, NCCN guidelines, and cancer organization- and health-related Web sites to identify single-agent therapies for MBC. All other drugs not on the above list that may have been used for breast cancer during the study period without FDA approval for this indication or NCCN recommendation would fall into the “other drug” category and would represent “off-label” use (e.g., bevacizumab, irinotecan).

<sup>b</sup> Listed as “other active chemotherapeutic agent” for treatment of MBC.

<sup>c</sup> Considered as targeted therapy and hence may not be listed in the “preferred single chemotherapeutic agent” category by NCCN.

<sup>d</sup> No patients in the present study cohort were administered the last 4 drugs. Epirubicin and thiotepa are FDA approved, and 1 drug (epirubicin) is listed in NCCN guidelines. Bleomycin and mitoxantrone are neither FDA approved nor NCCN recommended for breast cancer.

FDA = U.S. Food and Drug Administration; IM = intramuscular; MBC = metastatic breast cancer; NCCN = National Comprehensive Cancer Network.
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

Beth L. Nordstrom, PhD, MPH; Weixiu Luo, MD, MS; Kathy H. Fraeman, SM; Joanna L. Whyte, MS, RD, MSPH; and Robert J. Nordyke, PhD, MS

ABSTRACT

BACKGROUND: Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin alfa were indicated for use in chemotherapy-induced anemia to achieve target hemoglobin (Hb) levels of approximately 12 grams per deciliter (gm per dL), and treatment was to be withheld if Hb exceeded 13 gm per dL. In March 2007, the FDA changed the labeling of the ESAs to add boxed warnings, updated in November 2007, to include the following key points: (a) ESAs should be used only to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy; (b) treatment with ESAs should be stopped when chemotherapy ends; and (c) dosing ESAs to an Hb target of 12 gm per dL or greater has resulted in more rapid cancer progression or shortened overall survival in patients with breast, head and neck, lymphoid, cervical, and non-small cell lung malignancies. In January 2008, the FDA specified that the increased risk of more rapid tumor growth or shortened survival was associated with ESAs when “administered in an attempt to achieve a Hb level of 12 gm per dL or greater, although many patients did not reach that level.” A new black-box warning regarding this association was added to the labels of the ESAs in March 2008, and the FDA mandated further label changes on July 30, 2008, that ESA therapy should not be initiated in patients receiving chemotherapy at Hb levels of 10 gm per dL or higher.

OBJECTIVE: To (a) assess the prevalence and predictors of ESA administrations at Hb levels above 12 gm per dL among patients with a diagnosis of solid or hematologic cancer or myelodysplastic syndrome who began their first regimen of conventional myelosuppressive chemotherapy between 2002 and 2006, and (b) describe patterns of ESA treatment subsequent to the first ESA administration at Hb above 12 gm per dL.

METHODS: Using the Health Insurance Portability and Accountability Act (HIPAA)-compliant Varian Medical Oncology database of de-identified electronic medical records from 17 U.S. outpatient oncology practices, adults (aged 18 years or older) with any cancer diagnosis who began their first regimen of conventional myelosuppressive chemotherapy between January 1, 2002, and September 30, 2006, were identified. The Hb value associated with each ESA administration was defined as the closest Hb measurement within 7 days prior to the ESA administration. A first ESAHb > 12 was defined as the first time an ESA, either epoetin or darbepoetin, was given with an associated Hb greater than 12 gm per dL during the first chemotherapy regimen recorded in the database for each patient. Hb levels and ESA administrations after the first ESAHb > 12 were determined. Logistic regression models identified predictors of initial receipt of an ESAHb > 12, and of receiving further ESA treatment following the first such administration.

RESULTS: Between January 1, 2002, and September 30, 2006, there were 17,731 patients on chemotherapy, the mean (SD) age was 60 (13.2) years; 58.9% were female; 24.6% had breast cancer, 22.2% had lung cancer, 15.8% had colorectal cancer, 11.8% had hematologic cancer, and 25.6% had other or multiple cancers. Of these, 8,086 (45.6%) received an ESA at any time during the regimen, and 7,606 (42.9%) received an ESA at a known Hb level (i.e., Hb measurement within 7 days prior to ESA administration). During the first recorded chemotherapy regimen, 1,844 patients (10.4% of the chemotherapy cohort, 24.2% of ESA users with a known Hb; n=1,226 epoetin, n=618 darbepoetin) received an ESAHb > 12. Among patients receiving ESA treatment at a known Hb level, significant predictors of receiving an ESAHb > 12 included treatment in a community-based clinic rather than a hospital-affiliated clinic (odds ratio [OR]=2.96, 95% confidence interval [CI]=2.40-3.65), location of practice in the eastern United States (OR for Midwest=0.67, 95% CI=0.57-0.78; OR for West=0.27, 95% CI=0.22-0.34), hematologic cancer rather than solid tumor (OR=1.44, 95% CI=1.21-1.71), private health insurance (OR for public health insurance=0.80, 95% CI=0.70-0.93; OR for other/unknown insurance=0.54, 95% CI=0.47-0.62), and year of regimen 2002-2003 (ORs = 0.75, 0.74, and 0.71 for 2004, 2005, and 2006, respectively). Following the first ESAHb > 12, 276 (22.5%) of the patients on epoetin and 276 (44.7%) on darbepoetin received no further ESA treatment during the next 6 weeks (Pearson chi-square=96.1, P<0.001).

CONCLUSIONS: This analysis of outpatient oncology practices between 2002 and 2006 revealed that 24% of ESA users with a known Hb level received ESAHb > 12. Dose withholding subsequently occurred in 23%-45% of those patients. A higher proportion of patients on epoetin than darbepoetin continued ESA treatment after the first administration of ESAHb > 12.

What is already known about this subject

- Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin and darbepoetin were indicated for use in chemotherapy-induced anemia to a hemoglobin (Hb) level of approximately 12 grams per deciliter (gm per dL) and were to be withheld if Hb exceeded 13 gm per dL.
- At least 8 studies have shown that cancer patients with chemotherapy-induced anemia who received ESAs to a target Hb of more than 12 gm per dL have an increased risk of serious cardiovascular and thromboembolic events, mortality, and tumor progression.
- Starting in 2008, FDA label changes restricted initiation of ESAs to Hb below 10 gm per dL and use of the lowest dose of ESA necessary to avoid the need for a blood transfusion; if Hb exceeds a level needed to avoid transfusion, the ESA is to be withheld.
What this study adds

- Examination of the treatment patterns of ESA use in outpatient oncology practices during the years 2002-2006 prior to the FDA label changes indicated that less than 11% of chemotherapy patients, representing 24% of ESA users with a known Hb level, received an ESA at Hb exceeding 12 gm per dL (ESAHb>12).
- Among patients who were treated with an ESA at any time during the chemotherapy regimen and had a measured Hb level within 7 days prior to the ESA administration, 1,226 of 3,006 epoetin users (40.8%) and 618 of 4,600 darbepoetin users (13.4%) received at least 1 ESAHb>12.
- Following the first administration of ESAHb>12, ESA treatment was continued in 76.5% (950/1,226) of epoetin-treated patients and 55.3% (342/618) of darbepoetin-treated patients, a treatment pattern that was potentially allowable under 2002 guidelines but would violate 2008 labels and guidelines.
- Among chemotherapy patients treated with ESAs at a known Hb level, predictors of receiving an ESAHb>12 between 2002 and 2006 included treatment in a community-based clinic as compared with a hospital-affiliated clinic, practice location in the eastern United States as compared with the West and Midwest, hematologic cancer as compared with solid tumor, private health insurance, and receiving chemotherapy prior to 2004.

Many chemotherapeutic agents used in the treatment of cancer increase the risk of anemia. The development of anemia in cancer patients has been found to predict shorter survival times and may be associated with fatigue that negatively impacts quality of life. Chemotherapy-induced anemia can be treated either by red blood cell transfusions or with erythropoiesis-stimulating agents (ESAs). Epoetin alfa (epoetin) and darbepoetin alfa (darbepoetin) are currently the only ESAs marketed in the United States.

Prior to 2007, both ESAs were indicated for use in chemotherapy-induced anemia to target a hemoglobin (Hb) level of approximately 12 grams per deciliter (gm per dL); treatment was to be withheld if Hb exceeded 13 gm per dL. Studies have demonstrated an increased risk of adverse events and poor disease outcomes when ESAs were used for treatment of anemia in patients with cancer who were not on chemotherapy or when used to target a Hb level exceeding 12 gm per dL. As a result, the U.S. Food and Drug Administration (FDA) mandated label changes for both epoetin and darbepoetin, adding boxed warnings in March 2007 that were updated in November 2007 and again in July 2008. The new labeling in 2008 stated that (a) ESAs are “not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure,” (b) “therapy should not be initiated at hemoglobin levels >10 g/dL,” and (c) “Withhold Dose if: hemoglobin exceeds a level needed to avoid transfusion.” The ESA product label calls for discontinuation following completion of a chemotherapy course.

Because of findings of shortened survival and decreased time to progression of tumors in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers and increased risk of adverse cardiovascular and thromboembolic events, the ESA labels specify using the lowest dose necessary to avoid red blood cell transfusion and a target Hb range of 10 to 12 gm per dL. The boxed label warnings also emphasize that the use of ESAs to target Hb levels could potentially still be associated with increased risk of poor disease outcomes. Current guidelines from the American Society of Clinical Oncology/American Society of Hematology and the National Comprehensive Cancer Network state that ESA treatment should be discontinued if Hb shows little or no response (i.e., less than 1-2 gm per dL increase in Hb or no reduction in need for transfusion) within 6-8 weeks (see Appendix A).

The present retrospective study was designed to investigate patterns of ESA treatment and Hb levels among patients receiving the first chemotherapy regimen recorded in the database during the years 2002-2006. The goals of the study were to (a) quantify the prevalence and identify the predictors of receiving ESAHb>12 and (b) describe patterns of treatment following the first administration of ESAHb>12, in patients treated with chemotherapy and diagnosed with solid or hematologic cancer or myelodysplastic syndrome.

Methods

Data Source

The study data were obtained from the Varian Medical Oncology (Palo Alto, CA) database of electronic medical records (EMRs) from outpatient oncology practices. The database includes information on more than 150,000 cancer patients from 17 oncology provider organizations (13 community-based and 4 hospital-affiliated) comprising 71 clinic locations in the United States. At each patient visit to the clinic, the staff entered diagnoses, treatments, and other relevant information into the database. Diagnoses are entered as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, with no limit to the number that can be entered. Treatment data are entered as drug names and include orders or prescriptions for medications, with specifics such as dose and route, as well as duration of supply of oral medications and amount and timing of drugs administered in the clinic. Laboratory results were typically entered into the EMR...
system through an automated link with computerized data from the clinical laboratory; data include the date of the test, lab test name, result (Hb value to 1 decimal place; e.g., 12.1 gm per dL), units, and normal range. The data in the EMR system are limited to the treatments prescribed or administered in the oncology clinic and diagnoses that are addressed by the oncologist. Any medical care received in other settings, such as a hospital or other medical office, is unlikely to be noted in the database. The data used for the present study were de-identified, as required by the Health Insurance Portability and Accountability Act (HIPAA).

Cohort Definition

Eligible patients were adults (aged 18 years or older) who began their first regimen of conventional myelosuppressive chemotherapy identified in the database between January 1, 2002, and September 30, 2006. All included patients had a diagnosis of solid or hematologic cancer (ICD-9-CM codes 140-165.9, 170-176.9, 179-195.8, 199-208.91) or myelodysplastic syndrome (238.7) prior to or within 7 days after the start of the first chemotherapy regimen. These diseases include all cancer-related diagnoses found in patients administered ESAs in this database; not all diagnoses (e.g., myelodysplastic syndrome) are FDA-approved indications for ESA use. (A list of complete code descriptions is available upon request from the authors.) The first chemotherapy regimen was defined as the earliest treatment plan for each patient in the EMR system (treatment regimen file); records of administration of chemotherapeutic drugs without a specified treatment plan were excluded. Non-myelosuppressive cancer regimens, such as monoclonal antibodies in the absence of cytotoxic chemotherapy, were excluded.

Conventional myelosuppressive chemotherapies were those containing at least 1 cytotoxic chemotherapeutic agent; the most common regimens identified were carboplatin/paclitaxel, cyclophosphamide/doxorubicin, and fluorouracil/leucovorin/oxalplatin (FOLFOX). The treatment plans include text descriptions of the drugs in the regimen; these text descriptions were standardized and classified according to whether or not they contained at least 1 conventional myelosuppressive agent. Qualifying agents included arsenic trioxide, azacitidine, bleomycin, capcitabine, carboplatin, carmustine, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dexrazoxane, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, ifosfamide, irinotecan, mechlorethamine, melphalan, methotrexate, mitomycin, mitoxantrone, oxaliplatin, paclitaxel, pemetrexed, streptozocin, topotecan, vinblastine, vincristine, and vinorelbine.

Patients with the following characteristics were excluded from the analyses: (a) first systemic cancer regimen was not conventional myelosuppressive chemotherapy (e.g., hormonal therapy or biologic therapy alone), (b) planned cycle length was not specified in the database or was longer than 60 days, or (c) there was a gap of more than 6 months between any 2 antineoplastic drug administrations during the first regimen. One of the 17 oncology provider organizations had a substantial amount of missing data on chemotherapy administrations; thus, patients treated by this provider were also excluded from the study. Follow-up data for each patient were obtained through December 31, 2006.

ESA Exposure

We identified the dates and doses of all ESA administrations that occurred during each patient’s first chemotherapy regimen and found the closest Hb level measured on or within 7 days prior to the date of ESA administration. Because the analysis focused on treatment of chemotherapy-induced anemia and not anemia of cancer, only ESA administrations that occurred no more than 30 days after the most recent chemotherapy exposure were included. Patients who received at least 1 ESAHb>12 were identified, and the date of their first ESAHb>12 was noted. In a descriptive analysis of baseline demographic and clinical characteristics, the group of patients with ESAHb>12 was compared both with the full population of eligible patients on chemotherapy and with the subset of the full population that received an ESA during chemotherapy with a known Hb level; patients receiving ESAs with no known Hb level were excluded from the ESA group.

We looked for any further use during the chemotherapy regimen of ESAs following the first ESAHb>12 for each patient. The outcome measure included only ESA administrations that occurred within 30 days after chemotherapy and no more than 42 days apart. The 42-day restriction limited this analysis to ESA administrations that can be considered to fall within a single ESA episode of care. Up to 3 ESA administrations per patient following the first ESAHb>12 were examined. The closest Hb level within 7 days before each administration was noted.

Analysis

Baseline characteristics were summarized using the information available in the EMR database on or before the start of the first chemotherapy regimen. We constructed a logistic regression model using all patients receiving chemotherapy with at least 1 recorded Hb level to identify factors associated with receiving ESAHb>12. Variables entered into the model included age, gender, geographic region, year of regimen start, clinic type (community-based or hospital-affiliated), type of health insurance (private, public, or other/unknown), cancer type (solid, hematologic, or multiple), binary indicator for platinum-containing chemotherapy, and lowest Hb level during the first regimen (lowest on or before the first ESAHb>12 for those with at least 1 ESAHb>12). Patients lacking an Hb measurement at any time during the first regimen were excluded from the analysis.

A second logistic regression model, also examining receipt of ESAHb>12, included only patients who received at least 1 ESA with a known Hb level. Because all patients without the outcome included in this model had by design an Hb level less than or equal to 12 gm per dL, this model did not include lowest Hb level as a predictor. A third model, identical to the first with
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

**FIGURE 1** Flow Chart of Patient Selection and Classification

- **Total patients in chemotherapy treatment regimen file (N=27,450)**
  - First clinic visit not 1/1/2002-9/30/2006 (N=4,218, 15.4%)
  - No conventional myelosuppressive chemotherapy with start date 1/1/2002-9/30/2006 (N=910, 3.9%)
  - Cycle length of first regimen >60 days (N=340, 1.5%)
  - <18 years old at start of first regimen (N=36, 0.2%)
  - No cancer diagnosis 10 years before to 7 days after regimen start date (N=2,394, 10.9%)
  - ≥180 day gaps during the chemotherapy regimen (N=191, 1.0%)
  - Remove patients from site with missing administration data (N=1,630, 8.4%)

- **All cancer patients on chemotherapy (N=17,731)**
  - Patients with no ESA within 30 days after chemotherapy (N=9,645)
  - Patients with ESA at unknown Hb (N=480)

- **All chemotherapy patients with an ESA at known Hb (N=7,606)**
  - Patients with no ESA at Hb>12 gm per dL (N=5,762)

- **Patients with ESA associated with Hb >12 gm per dL (N=1,844)**
  - Epoetin (N=1,226)
    - Received further epoetin treatment (N=950)
    - No further ESA (N=276)
  - Darbepoetin (N=618)
    - Received further darbepoetin treatment (N=342)
    - No further ESA (N=276)

*ESA = erythropoiesis-stimulating agent; gm per dL = grams per deciliter; Hb = hemoglobin.*
respect to patients and variables entered, examined receipt of any ESA during the first chemotherapy regimen as an outcome. A final model sought factors associated with receiving further ESA treatment following the first ESAHb\(_{>12}\). This model included only the patients with at least 1 ESAHb\(_{>12}\) and contained the same variables as the first regression model, with the exception of using the Hb level associated with the first ESAHb\(_{>12}\) instead of the lowest Hb level, and adding the specific ESA given at first ESAHb\(_{>12}\) (epoetin or darbepoetin). All analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC).

**Results**

Of 27,450 patients who had provider-entered data on chemotherapy regimens in the treatment regimen file, we excluded those who started care in the oncology clinic outside of the study period, those lacking conventional chemotherapy or with unusual regimen data (i.e., recorded cycle length over 60 days or a gap in the regimen of at least 180 days), those younger than 18 years of age, those without a qualifying cancer diagnosis, and those who received care from the practice that did not adequately record drug administrations (Figure 1). We identified 17,731 patients who met all inclusion criteria.

Characteristics of all patients included in the cohort, all patients who received an ESA within 7 days of an Hb level measurement (n=7,606, 42.9%), and the group of patients who received an ESAHb\(_{>12}\) (n=1,844, 24.2% of ESA patients with known Hb value) are shown in Table 1. In the full cohort, ages ranged from 19-97, with a mean (SD) age of 60 (13.2); 58.9% were female; and 66.7% lived in the southern United States. Most had solid tumor types, with breast (24.6%), lung (22.2%), and colorectal (15.8%) the most common. The cancer types were, for the most part, similar to national distributions reported by Surveillance Epidemiology and End Results (SEER), except that lung cancer was more common and prostate cancer largely underrepresented in this database from outpatient oncology clinics.16

Of the full chemotherapy cohort of 17,731 patients, 8,086 (45.6%) received an ESA at any time during the regimen. At least 1 ESA associated with a known Hb level was administered to 7,606 patients (42.9%). A total of 1,844 patients (10.4% of the chemotherapy cohort, 24.2% of ESA users with a known Hb value) received at least 1 ESAHb\(_{>12}\). Of the patients with at least 1 ESAHb\(_{>12}\), the mean (SD) age was 62 (13.3); 63.7% were female; and 79.2% lived in the South. The distribution of tumor types was similar to that of the full cohort. Only 134 (7.3%) of the first ESAHb\(_{>12}\) administrations were associated with Hb exceeding 13 gm per dL. Among the 7,606 patients treated with an ESA at a known Hb level, 1,226 of 3,006 epoetin users (40.8%) and 618 of 4,600 darbepoetin users (13.4%) received at least 1 ESAHb\(_{>12}\).

The logistic regression model of all chemotherapy patients (Table 2, Equation 1) included 16,207 patients with known Hb levels during the chemotherapy regimen. The model revealed several significant (P<0.05) predictors of receiving at least 1 ESAHb\(_{>12}\). These included age 65 or older (odds ratio [OR]=1.21, 95% confidence interval [CI]=1.08-1.35), female gender (OR=1.27, 95% CI=1.14-1.41), residence in the eastern United States (OR for Midwest=0.55, 95% CI=0.47-0.64; for West=0.26, 95% CI=0.21-0.32), private health insurance (OR for public health insurance=0.74, 95% CI=0.65-0.84; for other/unknown insurance=0.49, 95% CI=0.43-0.56), visiting a community-based rather than hospital-affiliated clinic (OR=4.05, 95% CI=3.31-4.97), having a hematologic cancer rather than a solid tumor (OR=1.54, 95% CI=1.32-1.80), and receiving platinum-containing chemotherapy (OR=1.18, 95% CI=1.05-1.32). The lowest Hb level during the first regimen (prior to the first ESAHb\(_{>12}\)) date for patients with an ESAHb\(_{>12}\) was also associated with receiving at least 1 ESAHb\(_{>12}\); patients whose Hb fell below 11 gm per dL at any time during their regimen were most likely to receive ESAHb\(_{>12}\), whereas those whose Hb remained above 13 gm per dL at all times were unlikely to receive an ESAHb\(_{>12}\) (OR=0.17, 95% CI=0.12-0.24).

The model that included only the 7,606 patients who received an ESA with known Hb (Table 2, Equation 2) showed generally similar patterns but weaker effect sizes overall. In this model, there was no apparent effect of age (OR=0.99, 95% CI=0.88-1.11), female gender (OR=1.10, 95% CI=0.98-1.24) or platinum-based chemotherapy (OR=1.00, 95% CI=0.89-1.13). Significant predictors of receiving an ESAHb\(_{>12}\) included treatment in a community-based clinic rather than a hospital-affiliated clinic (OR=2.96, 95% CI=2.40-3.65), location of practice in the eastern United States (OR for Midwest=0.67, 95% CI=0.57-0.78; for West=0.27, 95% CI=0.22-0.34), hematologic cancer rather than a solid tumor (OR=1.44, 95% CI=1.21-1.71), private health insurance (OR for public health insurance=0.80, 95% CI=0.70-0.93; for other/unknown insurance=0.54, 95% CI=0.47-0.62), and year of regimen (2002-2003 (ORs=0.75, 0.74, and 0.71 for 2004, 2005, and 2006, respectively).

Compared with the first model of receiving at least 1 ESAHb\(_{>12}\) among all chemotherapy patients, predictors of receiving an ESA at any Hb level during the first regimen (Table 2, Equation 3) were generally similar, with a stronger effect of lowest Hb level and platinum-containing chemotherapy regimen, and a weaker effect of community-based clinic and geographic location in the western United States. Hematologic cancer showed no significant effect in this model (OR=0.93, 95% CI=0.81-1.06). The direction of the effect changed only with the year variables; receipt of any ESA showed a generally increasing pattern over time beginning in 2005.

The examination of the first 3 ESA administrations following the first ESAHb\(_{>12}\) showed that the likelihood of continued ESA treatment after the first ESAHb\(_{>12}\) was higher for epoetin than for darbepoetin. Following the first ESAHb\(_{>12}\), 276 (22.5%) of the patients on epoetin and 276 (44.7%) of those on darbepoetin received no further ESA treatment in the next 6 weeks (Pearson chi-square=96.1, P<0.001). Of the patients who received additional ESA treatment with a known Hb following the first ESAHb\(_{>12}\), Hb
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

### TABLE 1
Baseline Characteristics of Full Chemotherapy Cohort, Patients With Any ESA, and Patients With an ESA Associated With Hemoglobin Exceeding 12 Grams per Deciliter

<table>
<thead>
<tr>
<th>All Cancer Patients on Chemotherapy</th>
<th>All Chemotherapy Patients With an ESA at Known Hb</th>
<th>Patients With ESA Associated With Hb &gt; 12 gm per dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=17,731</td>
<td>n=7,606</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>7,290 (41.1%)</td>
<td>2,815 (37.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>10,437 (58.9%)</td>
<td>4,790 (63.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (0.0%)</td>
<td>1 (0.0%)</td>
</tr>
<tr>
<td>Age (years), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40</td>
<td>1,125 (6.3%)</td>
<td>417 (5.5%)</td>
</tr>
<tr>
<td>41-55</td>
<td>2,565 (14.5%)</td>
<td>979 (12.9%)</td>
</tr>
<tr>
<td>56-65</td>
<td>6,916 (39.0%)</td>
<td>2,731 (35.9%)</td>
</tr>
<tr>
<td>66 and older</td>
<td>7,125 (40.2%)</td>
<td>3,479 (45.7%)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>83 (0.5%)</td>
<td>10 (0.1%)</td>
</tr>
<tr>
<td>South</td>
<td>11,828 (66.7%)</td>
<td>5,297 (69.6%)</td>
</tr>
<tr>
<td>Midwest</td>
<td>2,425 (13.7%)</td>
<td>1,004 (13.2%)</td>
</tr>
<tr>
<td>West</td>
<td>3,392 (19.1%)</td>
<td>1,295 (17.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Insurance type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>3,890 (21.9%)</td>
<td>1,837 (24.2%)</td>
</tr>
<tr>
<td>Private</td>
<td>6,399 (36.1%)</td>
<td>3,079 (40.5%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>7,442 (42.0%)</td>
<td>2,690 (35.4%)</td>
</tr>
<tr>
<td>Clinic type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>3,932 (22.2%)</td>
<td>1,167 (15.3%)</td>
</tr>
<tr>
<td>Community</td>
<td>13,799 (77.8%)</td>
<td>6,439 (84.7%)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid - breast</td>
<td>4,368 (24.6%)</td>
<td>1,838 (24.2%)</td>
</tr>
<tr>
<td>Solid - lung</td>
<td>3,957 (22.2%)</td>
<td>1,994 (26.2%)</td>
</tr>
<tr>
<td>Solid - colorectal</td>
<td>2,805 (15.8%)</td>
<td>933 (12.3%)</td>
</tr>
<tr>
<td>Solid - head and neck</td>
<td>543 (3.1%)</td>
<td>210 (2.8%)</td>
</tr>
<tr>
<td>Solid - other</td>
<td>3,263 (18.4%)</td>
<td>1,430 (18.8%)</td>
</tr>
<tr>
<td>Hematologic - lymphoma</td>
<td>1,553 (8.8%)</td>
<td>679 (8.9%)</td>
</tr>
<tr>
<td>Hematologic - myeloma</td>
<td>262 (1.5%)</td>
<td>66 (0.9%)</td>
</tr>
<tr>
<td>Hematologic - leukemia</td>
<td>203 (1.3%)</td>
<td>74 (1.0%)</td>
</tr>
<tr>
<td>Hematologic - other</td>
<td>66 (0.4%)</td>
<td>45 (0.6%)</td>
</tr>
<tr>
<td>Multiple solid</td>
<td>577 (3.3%)</td>
<td>265 (3.5%)</td>
</tr>
<tr>
<td>Multiple hematologic</td>
<td>29 (0.2%)</td>
<td>14 (0.2%)</td>
</tr>
<tr>
<td>Multiple solid and hematologic</td>
<td>125 (0.7%)</td>
<td>58 (0.8%)</td>
</tr>
<tr>
<td>Hb level at first ESAHb&gt;12, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 - 13</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;13</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESA type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>NA</td>
<td>4,600 (60.5%)</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>3,006 (39.5%)</td>
<td>1,226 (66.5%)</td>
</tr>
</tbody>
</table>

ESA=erythropoiesis-stimulating agent; ESAHb>12=ESA administered at Hb exceeding 12 gm per dL; gm per dL=grams per deciliter; Hb=hemoglobin.

Levels exceeded 12 gm per dL at the next ESA administration for 437/885 (49.4%) of patients on epoetin and 127/319 (39.8%) of those on darbepoetin (Pearson chi-square=8.6, P=0.003); most of these administrations occurred at Hb ranging from more than 12 gm per dL to 13 gm per dL (37/1437 [84.9%] of epoetin and 106/127 [83.5%] of darbepoetin administrations at Hb exceeding 12 gm per dL). Overall, the 1,844 patients with an ESAHb>12 received a median of 2 additional ESA administrations following the first ESAHb>12.

The logistic regression model of receiving further ESA treatment after the first ESAHb>12 confirmed the between-drug difference in rates of continued ESA use (Table 3). After adjusting for measured baseline factors, receiving epoetin as the first ESAHb>12 remained a significant predictor of continuing ESA treatment, with an OR of 2.64 (95% CI=2.04-3.41).

### Discussion
This investigation of treatment patterns in outpatient oncology clinics in the United States revealed that during the years 2002-2006, 10.4% of chemotherapy patients observed, representing 24.2% of ESA users with known Hb levels, received ESAs at Hb levels exceeding 12 gm per dL at some time during their...
first chemotherapy regimen. Many factors were found to predict receiving at least 1 ESA_{Hb > 12}. The strongest effects were seen for community-based compared with hospital-affiliated clinics, perhaps because physicians in community-based clinics may be reimbursed directly for each ESA administration, but hospital-based clinics receive pooled reimbursement. Additionally, patients having at least 1 Hb less than 11 gm per dL at some point during chemotherapy were more likely to be treated at higher Hb levels than were patients whose Hb values were consistently greater than or equal to 11 gm per dL.

![Table 2: Logistic Regression Models of Receiving an ESA Associated With Hemoglobin Exceeding 12 Grams per Deciliter or Receiving Any ESA During First Chemotherapy Regimen](image-url)

- **Outcome Measure**: Receiving ESA at Hb > 12 gm per dL (All Chemotherapy Patients, N = 16,207)
- **EQUATION 1**: Predictors: Age (years), Gender, Clinic type, Type of cancer, Type of insurance carrier, Year of regimen start, Lowest Hb value.
- **EQUATION 2**: Predictors: Age (years), Gender, Clinic type, Type of cancer, Type of insurance carrier, Year of regimen start, Lowest Hb value.
- **EQUATION 3**: Predictors: Age (years), Gender, Clinic type, Type of cancer, Type of insurance carrier, Year of regimen start, Lowest Hb value.

**Predictor** | **EQUATION 1** | **EQUATION 2** | **EQUATION 3** |
---|---|---|---|
| Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval |
| **Age (years)** | | | | | | |
| 18 - 64 | 1.00 | | 1.00 | | 1.00 | |
| 65 and older | 1.21 | 1.08 | 1.35 | 0.99 | 0.88 | 1.11 | 1.43 | 1.31 | 1.56 |
| **Gender** | | | | | | | |
| Male | 1.00 | | | | | | |
| Female | 1.27 | 1.14 | 1.41 | 1.10 | 0.98 | 1.24 | 1.11 | 1.02 | 1.21 |
| **Clinic type** | | | | | | | |
| Hospital-affiliated | 1.00 | | | | | | |
| Community-based | 4.05 | 3.31 | 4.97 | 2.96 | 2.40 | 3.65 | 2.44 | 2.19 | 2.72 |
| **Geographic region** | | | | | | | |
| East^d | 1.00 | | | | | | |
| Midwest | 0.55 | 0.47 | 0.64 | 0.67 | 0.57 | 0.78 | 0.52 | 0.46 | 0.59 |
| West | 0.26 | 0.21 | 0.32 | 0.27 | 0.22 | 0.34 | 0.89 | 0.80 | 1.00 |
| **Type of cancer** | | | | | | | |
| Solid tumor | 1.00 | | | | | | |
| Hematologic cancer | 1.54 | 1.32 | 1.80 | 1.44 | 1.21 | 1.71 | 0.93 | 0.81 | 1.06 |
| Multiple primary cancers | 1.04 | 0.81 | 1.33 | 1.07 | 0.82 | 1.40 | 0.91 | 0.74 | 1.11 |
| **Type of insurance carrier** | | | | | | | |
| Private carrier | 1.00 | | | | | | |
| Public health insurance | 0.74 | 0.65 | 0.84 | 0.80 | 0.70 | 0.93 | 0.76 | 0.67 | 0.85 |
| Other or unknown insurance | 0.49 | 0.43 | 0.56 | 0.54 | 0.47 | 0.62 | 0.57 | 0.51 | 0.63 |
| **Year of regimen start** | | | | | | | |
| 2002-2003 | 1.00 | | | | | | |
| 2004 | 0.76 | 0.64 | 0.89 | 0.75 | 0.62 | 0.89 | 0.88 | 0.77 | 1.01 |
| 2005 | 0.86 | 0.74 | 0.99 | 0.74 | 0.63 | 0.87 | 1.33 | 1.17 | 1.51 |
| 2006 | 0.86 | 0.73 | 1.00 | 0.71 | 0.60 | 0.84 | 1.42 | 1.25 | 1.62 |
| **Lowest Hb value^e** | | | | | | | |
| <11 gm per dL | 1.00 | | | | | | |
| 11-12 gm per dL | 0.82 | 0.73 | 0.92 | 0.75 | 0.62 | 0.89 | 0.0.88 | 0.0.77 | 0.0.11 |
| >12-13 gm per dL | 0.75 | 0.64 | 0.87 | 0.74 | 0.63 | 0.87 | 0.0.3 | 0.0.03 | 0.0.03 |
| >13 gm per dL | 0.17 | 0.12 | 0.24 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| **Platinum-containing regimen** | | | | | | | |
| No platinum agents | 1.00 | | | | | | |
| Platinum agents | 1.18 | 1.05 | 1.32 | 1.00 | 0.89 | 1.13 | 1.33 | 1.21 | 1.45 |

^a C statistic for model = 0.73.
^b C statistic for model = 0.68.
^c C statistic for model = 0.86.
^d East included Northeast and South.
^e Lowest Hb value at any time during the chemotherapy regimen.

ESA = erythropoiesis-stimulating agent; gm per dL = grams per deciliter; Hb = hemoglobin.
ESA treatment was more likely to continue in patients whose Hb dropped below 12 gm per dL after the first ESA at Hb > 12, but still occurred in 25.9% of patients (1371+106)/1,844) when their Hb was between 12 and 13 gm per dL. These patterns are generally consistent with the prevailing guidelines for most of the study period, under which ESA treatment was initiated when Hb fell below 11 gm per dL, maintained to achieve an Hb of approximately 12 gm per dL, and withheld if Hb exceeded 13 gm per dL. Continuing ESA treatment after the first administration at high Hb levels occurred in 77% of patients on epoetin and 55% of those on darbepoetin. Patients on epoetin were more likely than those on darbepoetin not only to receive further ESA treatment, but also to have Hb again over 12 gm per dL at the time of the next ESA administration. Epoetin was administered to most patients on a weekly schedule and darbepoetin every 2 weeks. This difference in dosing schedule allows greater opportunity for further administrations of epoetin than darbepoetin during a given time window. To investigate the possibility that the restriction to a window of 30 days after the last chemotherapy administration could have biased the comparison between drugs with respect to further treatment, we conducted a sensitivity analysis using a 60- and a 90-day window after chemotherapy. The results using these 2 different time windows were essentially the same as those using a 30-day period. The 6-week follow-up duration for each patient allowed ample time for any further ESA treatment to appear, regardless of the original dosing schedule.

**Limitations**

To obtain an accurate picture of the treatment patterns occurring in oncology clinics, it is essential to use a database such as this EMR system rather than data from the tightly controlled environment of a clinical trial. Still, there are weaknesses inherent in these real-world data that one would not find in most controlled trials. First, Hb levels were not always measured or, in some cases, may have been measured but not entered into the EMR. Second, anemia-related symptoms may have prompted ESA treatment at these higher Hb levels and may explain some of the continued treatment seen, but information about symptoms was not consistently available in the database.

Third, red blood cell transfusions would also be expected to impact ESA treatment patterns, but again, these are not recorded reliably and, hence, were not examined in the present study. Because transfusions are indicated only at Hb levels well below 12 gm per dL, few if any members of the primary study group in the present analysis are likely to have received any transfusions following the first ESA administration at Hb over 12 gm per dL.

Fourth, while it is possible to identify ESA nonresponders in an EMR system through ESA and data for Hb levels, we did not examine these data, since the focus of the present study was on the use of ESAs at high Hb levels and not on inadequate Hb elevations in response to treatment.

Finally, we included all cancer-related conditions that were associated with actual ESA use rather than restricting to only the indicated uses, since the purpose of the present study was to investigate the actual use of these drugs as supportive care for patients on chemotherapy. For example, we included myelodysplastic syndrome (ICD-9-CM 238.7), a condition that is not

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**TABLE 3**  
Logistic Regression Model of Receiving Further ESA Treatment Following First ESA Associated With Hemoglobin Exceeding 12 Grams per Deciliter (N=1,844) 

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>65 and older</td>
<td>0.811</td>
<td>0.645 1.018</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.155</td>
<td>0.925 1.442</td>
</tr>
<tr>
<td><strong>Clinic Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-affiliated</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Community-based</td>
<td>2.577</td>
<td>1.655 4.012</td>
</tr>
<tr>
<td><strong>Geographic Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East‡</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>1.208</td>
<td>0.861 1.694</td>
</tr>
<tr>
<td>West</td>
<td>0.694</td>
<td>0.444 1.086</td>
</tr>
<tr>
<td><strong>Type of Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Hematologic cancer</td>
<td>1.257</td>
<td>0.910 1.737</td>
</tr>
<tr>
<td>Multiple primary cancers</td>
<td>1.508</td>
<td>0.876 2.596</td>
</tr>
<tr>
<td><strong>Type of Insurance Carrier</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private carrier</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Public health insurance</td>
<td>1.270</td>
<td>0.962 1.676</td>
</tr>
<tr>
<td>Other or unknown health insurance</td>
<td>1.162</td>
<td>0.871 1.548</td>
</tr>
<tr>
<td><strong>Year of first ESA at Hb&gt;12 gm per dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002–2003</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.775</td>
<td>0.540 1.113</td>
</tr>
<tr>
<td>2005</td>
<td>0.869</td>
<td>0.619 1.221</td>
</tr>
<tr>
<td>2006</td>
<td>0.737</td>
<td>0.527 1.031</td>
</tr>
<tr>
<td><strong>Platinum-containing regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No platinum agents</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Platinum agents</td>
<td>1.067</td>
<td>0.849 1.341</td>
</tr>
<tr>
<td><strong>Hb at first ESA at Hb&gt;12 gm per dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;13 gm per dL</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>&gt;12–13 gm per dL</td>
<td>1.346</td>
<td>0.909 1.992</td>
</tr>
<tr>
<td><strong>ESA at first ESA at Hb&gt;12 gm per dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>2.636</td>
<td>2.036 3.413</td>
</tr>
</tbody>
</table>

---

* C statistic for model = 0.66.  
* East included Northeast and South.  
ESA = erythropoiesis-stimulating agent; gm per dL = grams per deciliter; Hb = hemoglobin.
approved in FDA labeling of ESAs but that, when treated with chemotherapy, has been associated with use of ESAs in oncology practice.

Conclusions
We found that in the 5 years prior to product label changes made in 2007 and 2008, less than 11% of chemotherapy patients, representing 24% of all ESA users with a known Hb level, received an ESA at Hb levels above the 12 gm per dL upper end of the target range that was recommended during the study period. ESA treatment was subsequently withheld in 23% of epoetin users and 45% of darbepoetin users. Among ESA users with a known Hb level, factors predicting receipt of at least 1 ESA at Hb >12 were treatment in a community-based clinic, eastern region of the United States, private health insurance, and treatment year earlier than 2004. ESA use was more likely to continue following the first ESA at Hb >12 among patients treated with epoetin than among those treated with darbepoetin. With new product labels, the factors associated with initiation and continuing ESA administrations in chemotherapy-induced anemia as well as use in off-label indications warrant further investigation once sufficient data are available.

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DISCLOSURES
The study was conducted under a restricted contract with Amgen, which manufactures epoetin alfa and darbepoetin alfa. Whyte and Nordyke are employed by Amgen, and these 2 coauthors provided guidance and comments as well as contributed to the study concept and design. The principal author (Nordstrom) had final approval authority over the study design, analyses, and data interpretation.

Study concept and design were the work of Nordstrom, Nordyke, and Whyte. The data were extracted, managed, and analyzed by Fraeman and were interpreted primarily by Luo, Nordstrom, and Fraeman. The manuscript was written and revised primarily by Nordstrom.

REFERENCES
As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical, and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B12 deficiency where indicated, and assess for occult blood loss and renal insufficiency. Coomb’s testing may be appropriate for patients with chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and for those with a history of autoimmune disease; endogenous erythropoietin levels may predict response in patients with myelodysplasia. Consideration should be given to minimize use of erythropoiesis-stimulating agents (ESAs) in patients with high risk of thromboembolic events, as further discussed in Recommendation IV (below).

### Recommendations for chemotherapy-induced anemia

**I. General Recommendation**

2007 Recommendation

As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical, and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B12 deficiency where indicated, and assess for occult blood loss and renal insufficiency. Coomb’s testing may be appropriate for patients with chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and for those with a history of autoimmune disease; endogenous erythropoietin levels may predict response in patients with myelodysplasia. Consideration should be given to minimize use of erythropoiesis-stimulating agents (ESAs) in patients with high risk of thromboembolic events, as further discussed in Recommendation IV (below).

**II. Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin (Note: This Topic Is New to the Guideline)**

2007 Update Committee Statement

Based on a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia and on identical cancer-related indications, warnings, and cautions in the relevant U.S. Food and Drug Administration–approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.

### IIa. Chemotherapy-Induced Anemia: Threshold for Initiating ESA Therapy (Hemoglobin [Hb] Concentration Approaching or < 10 gm/dL)

2007 Recommendation

The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a Hb concentration that is approaching, or has fallen below, 10 gm/dL, to increase Hb and decrease transfusions. Red blood cell (RBC) transfusion is also an option depending on the severity of the anemia or clinical circumstances.

### IIb. Chemotherapy-Induced Anemia: Initiation Threshold > 10 gm/dL BUT < 12 gm/dL

2007 Recommendation

For patients with declining Hb levels but less severe anemia (those with Hb concentration < 12 gm/dL, but who have never fallen near 10 gm/dL), the decision of whether to use epoetin or darbepoetin immediately or to wait until the Hb levels fall closer to 10 gm/dL should be determined by clinical circumstances (including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic anemia, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living [ADLs]). RBC transfusion is also an option when warranted by clinical conditions.

### IV. Thromboembolic Risk (Note: This Topic Is New to the Guideline)

2007 Recommendation

Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbepoetin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Multiple myeloma patients who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids are at increased risk (Bennett et al., 2006). There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.
2007 Recommendation

V. Starting and Escalating Doses

The U.S. Food and Drug Administration-approved starting dose of epoetin is 150 U/kg three times per week or 40,000 U weekly subcutaneously. The U.S. Food and Drug Administration–approved starting dose of darbepoetin is 2.25 micrograms/kg weekly or 500 micrograms every 3 weeks subcutaneously. Alternative starting doses or dosing schedules have shown no consistent difference in effectiveness on outcomes including transfusion and Hb response, although they may be considered to improve convenience. Dose escalation should follow U.S. Food and Drug Administration–approved labeling (see table below); no convincing evidence exists to suggest that doses or dosing schedules have shown no consistent difference in effectiveness on outcomes including transfusion and Hb response, although they may be considered to improve convenience.

<table>
<thead>
<tr>
<th>Dose and Modifications</th>
<th>Epoetin Alfa</th>
<th>Darbepoetin Alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>150 U/kg SC TIW</td>
<td>40,000 U SC weekly</td>
</tr>
<tr>
<td>Dose increase</td>
<td>Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wks</td>
<td>Increase dose to 60,000 U SC weekly if no increase in Hb by &gt;1 gm/dL after 4 wks of therapy, in the absence of a RBC transfusion</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>Decrease dose by 25% when Hb reaches a level needed to avoid transfusion or Hb increases&gt;1 gm/dL in 2 wk</td>
<td>Decrease dose by 40% of previous dose when Hb reaches a level needed to avoid transfusion or Hb increases&gt;1 gm/dL in 2 wk</td>
</tr>
<tr>
<td>Dose withholding</td>
<td>If Hb exceeds 12 gm/dL, withhold dose until Hb approaches a level where transfusions may be required; restart dose at 25% below previous dose</td>
<td>If Hb exceeds 12 gm/dL, withhold dose until Hb approaches a level where transfusions may be required; restart dose at 40% below previous dose</td>
</tr>
</tbody>
</table>

ESA = erythropoiesis-stimulating agent; SC = subcutaneous; TIW = three times per week; Q3W = every 3 weeks; Hb = hemoglobin; wk = week; RBC = red blood cell.

VI. Discontinuing Therapy for No Response

2007 Recommendation

Continuing epoetin or darbepoetin treatment beyond 6 to 8 weeks in the absence of response (e.g., <1-2 gm/dL rise in Hb or no diminution of transfusion requirements), assuming appropriate dose increase has been attempted in nonresponders as per the U.S. Food and Drug Administration–approved label, does not appear to be beneficial, and ESA therapy should be discontinued. Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

VII. Hb Target

2007 Recommendation

Hb can be raised to (or near) a concentration of 12 gm/dL at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. Dose and dose modification recommendations recorded in the package insert as of March 2007 and approved by the U.S. Food and Drug Administration (also based on the November 8, 2007, FDA label announcement) can be found in the table above. Dose reductions are also recommended when Hb rise exceeds 1 gm/dL in any 2-week period or when the Hb exceeds 11 gm/dL. Risk of venous thromboembolism should also be considered when determining dose reduction schedules.

VIII. Iron Monitoring and Supplementation

2007 Recommendation

Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated, may be valuable in limiting the need for epoetin or darbepoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to ESA therapy. There is inadequate evidence to specify the timing, periodicity, or testing regimen for such monitoring. There is no change to the recommendation from the 2002 guideline.

IX. Anemia in Patients Not Receiving Concurrent Chemotherapy

2007 Recommendation

There is evidence that supports the use of epoetin or darbepoetin in patients with anemia associated with low-risk myelodysplasia. There are no published high-quality studies to support its exclusive use in anemic myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients in the absence of concurrent chemotherapy. Analyses of primary data from Study 20010103 (as yet unpublished) submitted to the U.S. Food and Drug Administration in March 2007 support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March 2007, as follows: “Use of ESAs increased the risk of death when administered to a target Hb of 12 gm/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population.”
X. Treatment of Anemia in Patients with Nonmyeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

2007 Recommendation

Physicians caring for patients with myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in Hb is not observed following chemotherapy, treatment with epoetin or darbopoetin for myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined previously. Particular caution should be exercised in the use of epoetin or darbopoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. (Refer to Recommendation IV.) Blood transfusion is also a therapeutic option. This recommendation is essentially unchanged from the 2002 guideline. Slight modifications to the recommendation appear in italics.

*Differences between the 2002 and 2007 guideline recommendations appear in italicized text.*
Self-Reported Use of Pharmaceuticals Among Patients With Irritable Bowel Syndrome in Primary Care

Áshild Faresjö, PhD; Ewa Grodzinsky, PhD; Saga Johansson, MD, PhD; Mari-Ann Wallander, PhD; Tomas Faresjö, PhD; and Toomas Timpka, MD, PhD

ABSTRACT
BACKGROUND: Irritable bowel syndrome (IBS) has an estimated 10%-12% prevalence in industrial countries. Studies from the United States have shown that IBS causes notable financial losses for employers. Due to the lack of pathophysiological markers, only a fraction of the pharmacological management of IBS has focused on etiological mechanisms. We hypothesized that there is a high consumption of nonspecific drugs among patients with IBS in their attempts to manage symptoms.

OBJECTIVE: To analyze self-reported use of prescription and over-the-counter (OTC) drugs among patients with IBS in primary care compared with controls from the general population.

METHODS: A population-based case-control design was used for the study. IBS cases were identified from the electronic medical records of 3 Swedish primary health care centers from January 1, 1997, through December 31, 2001. A questionnaire containing specific questions about prescription and OTC drugs was mailed in 2003 to 5,015 working-age (18-64 years) individuals (IBS cases and controls) in the Linköping IBS Population Study, a study of primary care patients with controls selected from the general population.

RESULTS: After 2 reminders, the overall response rate was 63% (3,074 respondents of 4,913 deliverable surveys); 71% responded for the IBS cases (347/486) and 57% (2,509/4,427) responded for the controls.

What is already known about this subject
- Due to the lack of pathophysiological markers in IBS, the majority of management practices are based on symptom relief. Use of psychotherapy, particularly cognitive behavioral therapy is well-studied with an estimated number needed to treat (NNT) of 2. However, there are no head-to-head trials of psychotherapy versus pharmacotherapy.
- Traditional medication frequently prescribed for IBS are dominated by the following drug classes: laxatives, gastrointestinal motility agents, antispasmodics, absorbents, and antiflatulents.
- Our previous research on a primary care population of 723 IBS cases based on medical records showed that patients with IBS appear not to be frequent users of health care services (only 37% had a follow-up visit with their primary care physician during a 5-year study period), and that the most commonly prescribed drugs were fiber and bulking laxatives 62.2%) and acid-suppressive drugs (23.1%).

What this study adds
- In a mailed survey using a population-based case design with controls from the general population, patients with IBS in primary care were 3 times more likely to report use of antidepressants and 9 times more likely to report use of acid-suppressive drugs.
- 11.5% of IBS patients self-reported visits to physicians for gastrointestinal complaints in the previous 3 months, compared with 1.9% of controls without IBS (P<0.001).

CONCLUSIONS: There was higher use of antidepressants among patients with IBS compared with controls from the general population. Even though they are not recommended for this patient category, the use of prescription and OTC acid-suppressive drugs is also common among IBS cases in primary care.

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biological factors may all play a role, although the impact of each of these factors on symptom development is likely to differ in patients and may vary over time for the same person. Because of the lack of pathophysiological markers in IBS, the majority of management practices has been based on symptom control. The interventions range from pharmaceutical treatment (e.g., antispasmodic and motility-regulating agents used alone or in combination with laxatives, antidiarrheal fiber therapy, or tricyclic antidepressants) to nondrug therapies (e.g., hypnotherapy, cognitive behavioral therapy). Use of psychotherapy, particularly cognitive behavioral therapy is the best studied psychological treatment of IBS, but there are no head-to-head trials of psychotherapy versus pharmacotherapy. Patients' self-assessments of their symptoms have therefore been recognized as important for the effective treatment of IBS.

Pharmacological interventions have supposedly been directed at the predominant symptoms, yet, to date, no single drug has been shown to have an effect on all of the multiple symptoms of IBS. Correspondingly, reports confirm that prescriptions for patients with IBS are dominated by 4 drug classes (in addition to laxatives): gastrointestinal motility agents, antispasmodics, absorbents, and antiflatulents. From a patient view, it is important that symptoms experienced are taken seriously so that treatment can be initiated early to avoid unnecessary suffering. The goal of treatment is generally to alleviate the symptoms of abdominal pain, altered bowel transit and any associated symptoms like fecal incontinence or bloating. The treatment approach should also be individualized and depend on the degree of symptoms from the different sub-classes of IBS. This trend is also seen in self-medication with over-the-counter (OTC) drugs, although the majority of patients with IBS receive prescription medications. While many drugs have been used in the treatment of IBS in the United States, only 2 drugs have been approved by the U.S. Food and Drug Administration specifically for this indication. Tegaserod (Zelnorm), a partial serotonin-4 receptor agonist, was voluntarily withdrawn from the U.S. market in March 2007 because of the risk of cardiovascular ischemic events. Since July 2007, tegaserod has been available to licensed health care providers in the United States through an investigational limited-access program within the following treatment protocol: (a) women aged younger than 55 years and (b) diagnosis of IBS with constipation or chronic idiopathic constipation.

Similarly, use of the serotonin-3-receptor antagonist alosetron (Lotronex) has been restricted because of side effects and is indicated only for women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy; in the United States, the patient must read and sign the patient-physician agreement prior to the initial prescription of alosetron. Use of tricyclic antidepressants in relieving IBS-related symptoms is controversial, but some studies suggest that overall global well-being may be improved.

Studies have also shown that approximately 50% of patients with IBS receiving care from primary care and specialist clinics have at least 1 comorbid somatic symptom, and patients with 1 or more comorbid somatic complaints tend to report more severe IBS symptoms, more mental complaints, and more illness-related absenteeism than patients without comorbid disorders. Comorbidity in other functional gastrointestinal conditions with overlapping symptoms might significantly affect the diagnosis and clinical management of IBS. The extent of self-therapy and the high prevalence of comorbid conditions warrant further investigation into the total consumption of pharmaceuticals in patients with IBS. Few studies exist concerning self-reported pharmacological treatment among IBS patients in primary care or in the general population. We therefore conducted a population-based case-control study addressing self-reported pharmacological treatment in patients with IBS. Our study, the Linköping IBS Population Study (LIPS), was conducted in the primary care setting and included a population-based control group.

The aim of our study was to examine self-reported pharmacological treatment with both prescription and OTC drugs among patients with IBS in primary care compared with controls without the disease from the general population, with particular emphasis on identifying the medications commonly used by patients diagnosed with IBS. Our primary hypothesis was that a high consumption of drugs not specifically indicated for use in IBS might occur in attempts by patients to control symptoms.

### Methods

#### Study Design

A population-based case-control design was used for the LIPS. Patients with IBS were recruited from Swedish primary health care centers on the basis of diagnoses stored in computerized medical records. Three primary health care centers were selected in Linköping, a city located in southeast Sweden with 135,000 inhabitants. These 3 health care centers serve a total study population of more than 40,000 inhabitants and are responsible for all primary health care consultations for the population in the area; only a negligible percentage of the population might visit other primary care providers. The control group was randomly selected from the population census register located in the same region as the primary health care centers. Before the investigation started, a pilot study was performed to develop a data collection form at 1 health care center. The medical records of 50 patients with IBS containing the code number K-58-p according to the International Classification of Diseases, Tenth Revision (ICD-10-P) were used for this purpose.

#### Data Collection

All cases with a recorded primary diagnosis of IBS (N=849) determined by the general practitioner were identified retrospectively in the electronic medical records over a 5-year period (January 1, 1997, through December 31, 2001). The ICD-10-P code K-58-p for IBS was used to identify the cases in the medi-
The number of controls was chosen proportionally according to the number of inhabitants living in the service areas of each of the 3 primary health care centers; up to 7 controls per case of IBS were used in this study. The questionnaire was mailed in 2003 to 5,015 potential study participants.

**Questionnaire**

We constructed a mail questionnaire based primarily on established and validated instruments measuring quality of life and mental problems. Additionally, we designed specific questions derived from regional and national surveys of welfare and health, life style and standard of living, sleep disturbance, and nutritional habits, as well as exercise regimens and the demands of and degree of control at work. Development of the questionnaire has been described elsewhere. Specific questions included self-reported current (2003) use of pharmacological treatment for gastrointestinal complaints, with a focus on drugs prescribed by physicians, OTC drugs, and physician visits within the past 3 months. Respondents were asked to report the name of the drug and whether the drug was prescribed by a physician or obtained OTC. Some prescription drugs (e.g., some nonsteroidal anti-inflammatory drugs [NSAIDs] in low doses [250 mg] and approximately half of the histamine-2 blockers as well as proton pump inhibitors) have become available as OTC agents in recent years in Sweden, as in the United States. Each self-reported medication was classified according to the Anatomical Therapeutic Chemical classification by the Nordic Councils on Medicines 1982 in Uppsala, Sweden, and the Swedish Drug Classification, FASS.

The mail questionnaire also included demographic data such as gender, civil status, educational level (primary school, secondary school, and upper secondary school classified as low educational level, university college and university classified as high educational level), and occupation. All questions were subsequently dichotomized in the database. Prior to the survey, a pilot study described elsewhere was performed.

The mail questionnaire was sent to 5,015 individuals in the LIPS population. Despite the checking of addresses prior to mailing, 29 patients with IBS and 73 controls had an unknown address or had died. A total of 4,913 individuals (486 IBS cases and 4,427 controls) remained in the final study group. After 2 reminders, the overall response rate was 64%; 72% (n = 351) responded for the IBS cases and 63% (n = 2,786) responded for the controls. Of these respondents, 59 controls and 4 patients with IBS refused to participate further in the survey. Consequently, remaining in the study were 347 IBS cases and 2,727 controls (Table 1). No difference was found in the severity of disease, defined as the proportion of referrals, between responders and nonresponders among the patients with IBS.

**Study Population**

The LIPS intended to study the impact of IBS on individuals in the working-age group; hence, only new cases of IBS in patients aged 18-64 years identified during the designated 5-year period were selected for this study. This process resulted in 515 cases of IBS identified in the primary care setting. The collection of data in the medical records of the IBS patients has been described elsewhere. By using the local census population register, 4,500 controls aged 18-64 years were randomly selected from the general population in the same geographical area as the IBS cases. The number of controls was chosen proportionally according to the number of inhabitants living in the service areas of each of the 3 primary health care centers; up to 7 controls per case of IBS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>IBS Cases, n</th>
<th>IBS Cases After Exclusion, n</th>
<th>Control Cases, n</th>
<th>Control Cases After Exclusion, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire mailed</td>
<td>515</td>
<td>4,500</td>
<td>4,500</td>
<td></td>
</tr>
<tr>
<td>Unknown address or deceased</td>
<td>–29</td>
<td>486</td>
<td>–73</td>
<td>4,427</td>
</tr>
<tr>
<td>Respondents (%)</td>
<td>351 (68.2%)</td>
<td>2,786 (61.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused to participate in study</td>
<td>–4</td>
<td>347</td>
<td>–59</td>
<td>2,727</td>
</tr>
<tr>
<td>Follow-up of possible GI diagnosis</td>
<td>–218</td>
<td>2,509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>among controls after study period ended</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final total</td>
<td>347 (67.4%)</td>
<td>2,509 (55.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Follow-up was conducted to ensure that controls were free from known GI diagnoses.*

GI = gastrointestinal; IBS = irritable bowel syndrome.
received a gastrointestinal diagnosis during the study period, and these individuals were subsequently excluded from further analysis. This check was made possible through information obtained from a population-based administrative health care database where all visits, including patient diagnoses in both primary and hospital care, are stored. (This database is a unique opportunity for the collection of data that defines medical care and health practices within the region [County Council of Östergotland]). The final study sample comprised 347 cases of IBS and 2,509 controls (Table 1).

Statistical Analysis
All data were stored in an SPSS database and statistically analyzed using the SPSS version 15.0 program (SPSS Inc., Chicago, IL). The significance of differences between the IBS cases and the control group for categorical variables was assessed using the Pearson chi-square test, and \( P < 0.05 \) was considered statistically significant. Bivariate (unadjusted) odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Bivariate correlation analyses were made using Spearman's correlations.

This study was approved in 2002 and in 2007 by the Ethical Committee at the Faculty of Health Sciences, Linköping University, Sweden.

Results
The majority of patients with IBS in the population studied were women, and more than 50% were under the age of 45 years. No significant differences were found concerning marital status or educational level among IBS cases compared with the control group. Cases with IBS had visited physicians more often in the past 3 months for gastrointestinal complaints than had controls (Table 2).

Unadjusted univariate correlation analyses revealed that prescription acid-suppressive drugs, fiber and bulking laxatives, antiflatulents, and anti-diarrhea drugs, as well as motility-regulating and antispasmodic drugs, were significantly more commonly used among cases with IBS compared with controls (Table 3). The difference was not as marked between the 2 groups for use of OTC drugs except for fiber and bulking laxatives, and the use of OTC drugs that were significantly more common among IBS cases also compared with that of the control group (OR = 10.31, CI = 5.85-18.16).

The self-reported current use of pharmaceuticals for other complaints showed that 4 prescribed drug classes were significantly more common among patients with IBS compared with controls in this study: antidepressants (OR = 3.27, CI = 2.27-4.70), sedative-hypnotics (OR = 2.49, CI = 1.44-4.29), analgesics such as paracetamol (acetaminophen) (OR = 2.86, CI = 1.88-4.33), and thyroid hormones (OR = 2.43, CI = 1.39-4.26) (Table 3).

Discussion
In this study, we identified prescription and OTC pharmaceuticals used by patients with IBS in the primary care setting. This knowledge can be used both to avoid polypharmacy by adapting general drug therapy recommendations and as input for the determination of etiological mechanisms involved in the syndrome.

Baseline data for this study (from medical records) showed that 6.5% of the IBS cases had documented receipt of antidepressants in their medical records and that all of these IBS patients also had a diagnosis of depression or anxiety documented in their records. However, from the follow-up questionnaire distributed 2 years later, 13.3% of patients with IBS reported use of antidepressants, reflecting an increase in antidepressant use among these patients. This trend in the use of antidepressants is in accordance with findings from other studies. The increased use of antidepressants may reflect a growing interest to use this category of drugs for modulation of gut sensory-motor function and pain in IBS. An alternative explanation is that there is an increased awareness among primary care physicians of the comorbidity of IBS and psychiatric disease. In this context, it can be noted that antidepressants were not included in the common set of pharmaceuticals used for patients with IBS (Table 3). Further studies on antidepressant use among IBS patients are thus warranted, while also taking into consideration the reports stating that the attitudes and practice models of physicians toward this patient...
group differ depending on practice speciality. They observed a high use of acid-suppressive drugs, despite the recommended pharmaceutical treatment of IBS involving fiber and bulking laxatives, antidiarrheals, and antiflatulents drugs combined with changes in food habits, depending on the type of IBS symptoms (IBS-C, IBS-D, IBS-A). The use of acid-suppressive drugs by patients with IBS may reflect dissatisfaction with current IBS therapies or the existence of gastrointestinal comorbidity (e.g., dyspepsia or gastroesophageal reflux disease). We did not explore the reasons for use of acid-suppressive drugs among IBS patients.

Use of analgesics, such as acetylsalicylic acid drugs and other NSAIDs, can result in a worsening of IBS symptoms and an increased risk of developing upper gastrointestinal side effects. The results of the present study reflect the IBS treatment paradigm in use today (i.e., symptom relief). However, nondrug therapies, such as hypnotherapy and cognitive behavioral therapy, are being employed with increasing frequency. Explaining to patients how to cope with IBS and manage everyday life, establish regular bowel habits, and avoid certain foods and stress will remain an important clinical protocol for physicians. As was also shown by the results of our study, drug therapy can be regarded as more or less helpful for IBS patients. Recent pharmacological approaches that exploit the expanding knowledge of the brain-gut axis as well as different neurotransmitters and receptors have revealed numerous new therapeutic targets. For instance, drugs

### Table 3: Self-Reported Use of Pharmaceuticals Among Patients With Irritable Bowel Syndrome in Primary Care

<table>
<thead>
<tr>
<th>Fueling use:</th>
<th>IBS</th>
<th>Controls</th>
<th>r</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescription Drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid-suppressive drugs</td>
<td>13.3 (46%)</td>
<td>1.6 (41%)</td>
<td>0.221</td>
<td>9.20</td>
<td>5.94-14.25b</td>
</tr>
<tr>
<td>Fiber and bulking laxatives</td>
<td>4.9 (17)</td>
<td>0.5 (12)</td>
<td>0.144</td>
<td>10.72</td>
<td>5.07-22.64b</td>
</tr>
<tr>
<td>Antidiarrheals</td>
<td>2.9 (10)</td>
<td>0.0 (1)</td>
<td>0.150</td>
<td>74.42</td>
<td>9.49-583.21b</td>
</tr>
<tr>
<td>Motility agents/antispasmodics</td>
<td>1.7 (6)</td>
<td>0.1 (2)</td>
<td>0.102</td>
<td>22.06</td>
<td>4.43-119.72b</td>
</tr>
<tr>
<td>Antiflatulents</td>
<td>1.4 (5)</td>
<td>0.0 (1)</td>
<td>0.100</td>
<td>36.67</td>
<td>4.27-314.79b</td>
</tr>
<tr>
<td>Antacids</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alginates</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IBD drugs</td>
<td>0.3 (1)</td>
<td>0.1 (3)</td>
<td>−0.015</td>
<td>2.41</td>
<td>0.25-23.27</td>
</tr>
<tr>
<td><strong>Pharmaceuticals for gastrointestinal complaints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid-suppressive drugs</td>
<td>13.3 (46)</td>
<td>1.6 (41)</td>
<td>0.221</td>
<td>9.20</td>
<td>5.94-14.25b</td>
</tr>
<tr>
<td>Fiber and bulking laxatives</td>
<td>4.9 (17)</td>
<td>0.5 (12)</td>
<td>0.144</td>
<td>10.72</td>
<td>5.07-22.64b</td>
</tr>
<tr>
<td>Antidiarrheals</td>
<td>2.9 (10)</td>
<td>0.0 (1)</td>
<td>0.150</td>
<td>74.42</td>
<td>9.49-583.21b</td>
</tr>
<tr>
<td>Motility agents/antispasmodics</td>
<td>1.7 (6)</td>
<td>0.1 (2)</td>
<td>0.102</td>
<td>22.06</td>
<td>4.43-119.72b</td>
</tr>
<tr>
<td>Antiflatulents</td>
<td>1.4 (5)</td>
<td>0.0 (1)</td>
<td>0.100</td>
<td>36.67</td>
<td>4.27-314.79b</td>
</tr>
<tr>
<td>Antacids</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alginates</td>
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</tr>
<tr>
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<td>0.3 (1)</td>
<td>0.1 (3)</td>
<td>−0.015</td>
<td>2.41</td>
<td>0.25-23.27</td>
</tr>
<tr>
<td><strong>Pharmaceuticals for other complaints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>13.3 (46)</td>
<td>4.5 (112)</td>
<td>0.126</td>
<td>3.27</td>
<td>2.27-4.70b</td>
</tr>
<tr>
<td>Analgesics</td>
<td>9.5 (33)</td>
<td>3.5 (89)</td>
<td>0.096</td>
<td>2.86</td>
<td>1.88-4.33b</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>9.5 (33)</td>
<td>7.6 (191)</td>
<td>0.023</td>
<td>1.28</td>
<td>0.86-1.87</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>8.6 (30)</td>
<td>8.4 (210)</td>
<td>0.003</td>
<td>1.04</td>
<td>0.69-1.55b</td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>6.9 (17)</td>
<td>7.6 (191)</td>
<td>0.023</td>
<td>1.28</td>
<td>0.86-1.87</td>
</tr>
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<td>0.003</td>
<td>1.04</td>
<td>0.69-1.55b</td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>5.2 (18)</td>
<td>3.7 (93)</td>
<td>0.025</td>
<td>1.42</td>
<td>0.84-2.38</td>
</tr>
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<td>Antimalarials</td>
<td>6.9 (17)</td>
<td>2.2 (54)</td>
<td>0.063</td>
<td>2.49</td>
<td>1.44-4.29b</td>
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<td>Thyroid hormones</td>
<td>9.5 (33)</td>
<td>2.1 (52)</td>
<td>0.060</td>
<td>2.43</td>
<td>1.39-4.26b</td>
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<td>Lipid-lowering drugs</td>
<td>9.5 (33)</td>
<td>3.3 (84)</td>
<td>0.012</td>
<td>1.21</td>
<td>0.68-2.16</td>
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<td>Anticoagulants</td>
<td>3.2 (11)</td>
<td>3.3 (84)</td>
<td>−0.003</td>
<td>0.95</td>
<td>0.49-1.79</td>
</tr>
<tr>
<td>Diabetes mellitus drugs</td>
<td>1.6 (6)</td>
<td>1.5 (38)</td>
<td>0.006</td>
<td>1.14</td>
<td>0.48-2.72</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1.2 (4)</td>
<td>1.0 (25)</td>
<td>0.005</td>
<td>1.16</td>
<td>0.40-3.34</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>0.6 (2)</td>
<td>0.1 (3)</td>
<td>0.03</td>
<td>0.23-4.56</td>
<td></td>
</tr>
<tr>
<td>Other drugs</td>
<td>19.6 (68)</td>
<td>12.3 (308)</td>
<td>0.071</td>
<td>1.74</td>
<td>1.30-2.33b</td>
</tr>
</tbody>
</table>

*P < 0.05 calculated by the Pearson chi-square test.

*P < 0.001 calculated by the Pearson chi-square test.

Examples of antacids and alginate include Novalucul, Rennie, Limin and Gaviscon.

Examples of IBD drugs include meselamine delayed-release (Asacol), sulfasalazine (Azulfidine, Salazopyrin), meselamine (Pentasa, Mesacol), and balsalazide (Colazal, Colazid).

Examples of antidepressants include angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics.

Examples of other drugs include contraceptives and vitamins.

CI = confidence interval; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; OTC = over-the-counter; r = Spearman's correlation coefficient.
in current development include new serotonergic agents and anti-
depressants, various central, peripheral, and autonomic neural
receptor ligands, and gut immune modulators.41,42 Also, probiotics
that are based on lactobacilli and bifidobacteria, for example, seem
to offer an option for alleviating IBS symptoms.43-45 Probiotics
work by restoring both qualitative and quantitative alterations in
the intestinal flora. This insight promises further progress in the
treatment of IBS, hopefully in the primary care setting where the
majority of IBS cases are diagnosed.

Recently published studies of the IBS population of the LIPS
(all ages) concerning the drug prescription patterns of general
practitioners have shown that fiber and bulking laxatives, along
with acid-suppressive drugs, were the most frequently prescribed
(62.2% and 23.1% respectively) drug categories.30 These data con-
trast somewhat with data from other studies that reported anti-
spasmodic, motility-regulating, anti-diarrhea, and antiflatulent
drugs as the most frequently prescribed medications to patients
with IBS in primary care.11,14 By using data obtained from ques-
tions concerning the current actually used pharmaceuticals, our
study confirms this to some extent by demonstrating that 13.3%
of patients with IBS actually use fiber and bulking laxatives,
whether prescribed (4.9%) or OTC (8.4%), while 15.0% use either
prescribed (13.3%) or OTC (1.7%) acid-suppressive drugs.

Among the drug classes used for abdominal complaints, all
except the prescription IBD drugs (e.g., sulfasalazine) and OTC
antacids were more commonly used by IBS patients compared
with controls. However, the absolute counts of patients reporting
use of most categories of drugs for abdominal complaints are small (e.g., only 6 patients [1.7%] reported use of motility/
antispasmodic agents). Prescription antiflatulents and anti-diar-
rhreas, as well as motility-regulating and antispasmodic drugs,
were significantly more commonly used among IBS cases com-
pared with controls, possibly because diarrhea and cramps (pain/spasms) are common features of IBS. However, these
same drugs (antiflatulents, anti-diarrheas, motility-regulating
and antispasmodic drugs) were self-reported by relatively few IBS
survey respondents, thus making these particular results more
uncertain. General recommendations for the use of drugs in IBS
is directed toward the most troublesome symptoms.13,14 Because
the theoretical aim of pharmaceutical therapy is to modulate
supposed physiological mechanisms and eradicate symptoms,13
the pharmaceutical treatment patterns identified in our survey
research suggest that the scope of symptom relief is wide in
patients with IBS.

Limitations
Our results concerning the use of OTC drugs must be evaluated
in light of their availability, which may vary between countries.
Although strong restrictions have been placed on OTC drug dis-
tribution in Sweden in the past, recent years have witnessed an
increase in the number of available OTC drugs.36

Although we surveyed patients with IBS and controls regard-
ing their current (2003) use of prescription and OTC drugs, our
survey was conducted among patients with diagnoses that were
recorded up to 6 years previously (in 1997). Therefore, some
patients in the IBS group might not have had IBS symptoms at
the time that our survey was conducted.

The diagnosis of IBS was based on medical records from
general practitioners. Because general practitioners might not be
considered to be experts in the diagnostic criteria for IBS, it is
possible that some IBS patients were given false-positive diag-
noses. However, studies have shown that general practitioners
rarely misdiagnose IBS,46-49 in fact, there may be a tendency to
underdiagnosis IBS in primary care. However, the potential for
a false-negative diagnosis of IBS is not directly relevant to this
study because it was not our primary purpose to determine the
prevalence of IBS. Finally, we did not categorize the use of anti-
depressants by type (i.e., tricyclic antidepressants, selective sero-
tonin-reuptake inhibitors, or serotonin-norepinephrine reuptake
inhibitors). This additional descriptive information might have
informed the question about specific antidepressant use among
patients with IBS.

Conclusions
Use of antidepressants is higher among patients with IBS in pri-
mary care compared with controls from the general population.
Although not recommended for the treatment of IBS symptoms,
use of prescription and OTC acid-suppressive drugs is also com-
mon. Further studies of IBS medication patterns in the primary
care setting are warranted.

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Study concept and design were contributed primarily by Åshild Faresjö and Ewa Grodzinsky. Åshild Faresjö performed the largest share of the data collection. All authors contributed to data interpretation, which was led by Åshild Faresjö and Tomas Faresjö. All authors contributed to writing and revision of the manuscript.

REFERENCES
COMMENTARY

A Bleak Future for Independent Community Pharmacy Under Medicare Part D

Joshua J. Spooner, PharmD, MS

The Medicare Part D prescription drug program was implemented in 2006 to provide prescription drug coverage for elderly and disabled citizens. Recent data indicate that Part D provides prescription drug coverage for 3.4 million American seniors who did not otherwise have prescription insurance. Analyses of prescription claims data suggest that Part D has increased prescription drug utilization among Medicare recipients by 3.9% to 12.8%, and survey data have demonstrated that Part D has led to a small but significant decrease in the percentage of Medicare recipients who were nonadherent with their medication because of cost. Seniors are generally happy with Part D, and while there are no survey data to document the opinions of those representing pharmaceutical manufacturers and Part D prescription drug plans, it is probable that they are pleased with the current state of Part D as well. It seems that all of the parties with a direct interest in Part D are benefiting from the program—all except for one group.

A Shifting Customer Mix, Increased Administrative Burden, and Delays in Payment

The business of pharmacy has undergone significant changes following the implementation of Part D. Gross margins on prescriptions covered by Part D tend to be lower than those prescriptions covered by Medicaid, commercial health insurers, or cash customers; following Part D implementation, pharmacies have faced reduced payments due to a change in their customer case-mix. While prescription volume among Medicare beneficiaries has increased under Part D, the size of the increase at some pharmacies has been less than anticipated, in part because 86% of Part D beneficiaries had prescription drug coverage in the year before enrolling in Part D through commercial insurers, Medicaid, or multiple sources. The movement of pharmacy customers into Part D programs increases the likelihood that prescriptions for maintenance medications will be handled by mail order pharmacies, reducing the increase in prescription volume at community pharmacies. Further, the enrollment of some cash customers into Part D has not only brought a reduction in payment for these previously high-margin prescriptions, but also forces pharmacies to wait for payment from the prescription drug plan (as opposed to payment at the time of purchase by a cash customer), creating or augmenting cash flow issues for pharmacies.

The implementation of Part D has been particularly tough on independent community pharmacies. The clientele of independent pharmacies is older than those who frequent other types of community pharmacies; customers of independent pharmacies are nearly twice as likely as the average pharmacy customer to be eligible for Part D. As such, the conversion rate of prescriptions to Part D payment is likely to be higher in independent pharmacies than other community pharmacies. During the open enrollment period of November and December 2006, independent pharmacies reported spending an average of 4.5 hours each day dealing with administrative issues related to Part D (such as contracting with Part D prescription drug plans and answering patient questions on Part D plan choices, formularies, and costs). While many pharmacist-owners or their paid staff performed the majority of this work themselves, it displaced their usual activities, leaving them with less time for filling prescriptions, counseling patients, bookkeeping, and managing their inventory. In many instances, independent pharmacists were required to extend their workday to complete their work. This time expenditure places independent pharmacies at a competitive disadvantage relative to chain pharmacies, where most of the administrative issues related to Part D are handled by staff at corporate headquarters, and store pharmacists can refer patients to company-developed online tools to help seniors compare prescription drug plans.

Although the number of prescriptions dispensed has increased since the implementation of Part D, gross margins are down, indicating that the average community pharmacy is doing more while making less money. Independent pharmacies do not typically generate the front store revenue necessary to offset this loss in prescription gross margins. Few independents can match the size of the chain pharmacy, where new stores average 13,000 to 14,500 square feet and allow front store sales to account for 30%-35% of revenues. This proportion stands in sharp contrast to the findings of a recent survey of rural independent pharmacies, where front store sales accounted for no more than 15% of revenues at nearly 80% of the surveyed pharmacies, and no more than 5% of revenues at an astonishing 31% of pharmacies.

Independent pharmacies have also been negatively impacted by the slow payment times from Part D prescription drug plans. In an analysis by Shepherd et al., independent pharmacies had a slower median time to payment following adjudication by Part D plans compared with chain pharmacies in 2006 (31 days vs. 29 days). Further, delays in payment have increased the cash flow issues faced by independent pharmacies, forcing them to borrow more from their lines of credit, which now average over
A Bleak Future for Independent Community Pharmacy Under Medicare Part D

$70,000 per store.¹⁵ Interest payments on these credit lines erode the pharmacy’s operating margin, leaving less money available for paying salaries, marketing, and capital investments. While Part D creates cash flow issues for all pharmacies, chain pharmacies have access to cash on hand and a variety of financing mechanisms to help them manage their accounts receivable that most independent pharmacies do not have.

Medicaid Reimbursement and Other Business Threats

Independent pharmacies face challenges beyond Part D. The ongoing pharmacist shortage has driven up salaries,¹⁶ making it more expensive for independent pharmacy owners to employ additional pharmacists or hire relief pharmacists. The decision by some discount retailers¹⁷,¹⁸ and chain pharmacies¹⁹,²⁰ to offer cash customers hundreds of generic medications at a price of $4 for a 30-day supply or $10 for a 90-day supply has forced independent pharmacies to make the difficult decision whether to match that price (and accept a lower gross margin on these high-margin prescriptions) or risk losing customers (and all of their prescriptions) to a competitor. As a result of the Deficit Reduction Act of 2005,²¹ the federal upper limit on Medicaid reimbursement for multisource generic products, currently tied to average wholesale price, may become tied to average manufacturer price (AMP). If this change is implemented as initially designed, the Government Accountability Office (GAO) estimates that the Medicaid reimbursement rate for multisource generics would be an average of 36% below the acquisition cost.²² Lastly, under an Internal Revenue Service (IRS) rule set to take effect in 2009, pharmacies are required to have an inventory information approval system (IIAS) to process debit cards for flexible spending accounts and health reimbursement arrangements.²³ While pharmacies that have 90% or more of their gross receipts come from items that qualify as medical expenses under IRS code are eligible for a waiver from the IIAS requirement (an estimated 78% of independent pharmacies qualify for this exemption²⁴), credit card companies have not developed a process to recognize stores that qualify for this exemption.²⁵ This problem leaves many independent pharmacies with another difficult choice: purchase an IIAS-compliant point of sale system (at a cost of $8,000 to $30,000), or hope that a solution is developed to recognize pharmacies eligible for the exemption before the IRS rule goes into effect.

All of the above factors have made owning and operating independent community pharmacies very challenging. According to the National Community Pharmacists Association (NCPA), the number of independent community pharmacies in operation in the United States during 2006 fell from 24,500 to 23,348, a 5% decline.⁶ As the number of independent pharmacies had remained at a stable level in the years leading up to the implementation of Part D, observers have speculated that Medicare Part D was the factor responsible for this large decrease in the number of independent pharmacies.²⁵ Further, 22% of respondents to a survey of independent pharmacies reported their pharmacy’s financial position as declining, poor, or unstable following the first year of Part D.⁸

Evaluation of Economic Model of Medicare Part D in Independent Community Pharmacy

In the October 2008 issue of JMCP, Carroll²⁶ reported the results of a financial model using data from NCPA’s survey of independent pharmacies²⁷ and IMS Health national market research data¹ in order to estimate the impact of Part D on the profitability of independent pharmacies. This model is an excellent resource for those seeking to understand the effects of Part D on community pharmacies, and its findings are likely to be of interest to health economists, policy analysts, pharmacy trade groups, and others. The author should be commended for creating such a finely crafted and worthwhile tool. The model estimated that although Part D led to a modest 0.4% increase in prescription volume for the typical independent pharmacy, the lower Part D reimbursement rate led to an absolute decline in the gross margin for all prescriptions of 0.7% and a mean decrease in net income before taxes of 22%, or $27,651. In the sensitivity analyses that accompanied his analysis, Carroll found no scenario in which the net profit increased for the typical independent pharmacy as a result of Part D.

Due to the limitations of available data (point estimates without measures of error), the model was forced to rely upon the mean values for revenues, expenses, and prescription volume obtained from a national sample of independent pharmacies.²⁷ One potential limitation of mean values is that they can be skewed by outliers; for example, while the mean salary for major league baseball players in 2008 was $3.15 million, the median salary was $1 million, greater than a 3-fold difference.²⁸ While Carroll’s model utilized a baseline value of $3.49 million for annual sales at the typical independent pharmacy, this mean value may have been driven up by a small group of high-performing stores; as such, annual sales at a “truly typical” independent pharmacy (as measured by the median value) may be substantially lower. If and when median data become available, it may be of interest to run the analysis again using median values for revenues, expenses, and prescription volumes, and examining the degree to which the model results change. When run with mean values, the model found that the typical independent pharmacy remained profitable following Part D implementation, even under the least favorable conditions. Substituting median values may produce some scenarios in which independent pharmacies were no longer profitable following Part D implementation, something that occurred in reality in 2006 with a net loss of 1,152 stores nationwide.⁶

Carroll uses the results of his model and other evidence²⁹ to suggest that the profitability of the physical act of dispensing prescriptions will continue to decline for community pharmacies, and that the future of community pharmacy lies less in dispensing and more in patient care services such as medication...
therapies such as medication therapy management (MTM). While there is no question that the profitability of dispensing prescriptions has lessened significantly, it is unclear if patient care services can help improve the balance sheet of independent pharmacies. A survey of independent pharmacies offering MTM services found that only 42% of respondents thought that MTM services were profitable given the resources necessary to provide the service.8 Further, independent pharmacies face several obstacles in incorporating patient care services into their practice. Many independent pharmacies are staffed by a single pharmacist, who may not be able to take time away from his or her customary activities in order to devote time to patient care services. Smaller pharmacies may lack the space needed for patient care areas, while pharmacies of all sizes may have physical barriers that may impede patient care activities.30 Additionally, some pharmacists may feel that they do not have sufficient training or expertise in patient care activities to offer them. In a survey of independent community pharmacists, the most frequently cited reasons for not offering MTM services were time or staffing constraints, a lack of private space, the time requirements for mandatory training/certification, and beliefs that reimbursements for MTM services were too low.8

More Attention is Needed

Despite all of the challenges facing independent community pharmacies, there have been some recent developments that might point to better days ahead. After a significant decline in 2006, the number of independent community pharmacies operating in the United States stabilized in 2007.31 In July 2007, Congress overrode President George W. Bush’s veto and passed The Medicare Improvements for Patients and Providers Act,32 which included provisions to (a) require Part D prescription drug plans to reimburse pharmacies within 14 days of claim adjudication starting January 1, 2010; and (b) delay the implementation of the AMP pricing formula for generic Medicaid prescriptions until September 2009, allowing Congress to modify the reimbursement formula in light of the recent GAO report.22 Congress is also considering The Community Pharmacy Fairness Act,33 which would create an exemption to antitrust laws allowing independent pharmacies to collectively negotiate contract terms with pharmacy benefit managers. Aside from interest pieces in local newspapers33,34 and the lobbying efforts of NCPA, the effect of Part D on the independent community pharmacy has given largely unnoticed. A quote from Arthur Miller’s Death of a Salesman seems appropriate: “I don’t say he’s a great man. Willy Loman never made a lot of money. His name was never in the paper. He’s not the finest character that ever lived. But he’s a human being, and a terrible thing is happening to him. So attention must be paid. He’s not to be allowed to fall into his grave like an old dog. Attention, attention must be finally paid to such a person.”35 It is time attention is given to independent pharmacy owners. They provide valued services to their clientele, and in many instances operate the only pharmacy within a community.36 The closure of an independent pharmacy not only affects the business owner and his or her staff, but can also mean the end of convenient access to pharmacy services for patients, including the very Medicare beneficiaries for whom Part D was created.

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DISCLOSURES


REFERENCES

A Bleak Future for Independent Community Pharmacy Under Medicare Part D


Irritable Bowel Syndrome and Antidepressants

Frederic R. Curtiss, PhD, RPh, CEBS

In this issue of JMCP, Faresjö and colleagues found that 13.3% of patients with irritable bowel syndrome (IBS) reported using antidepressants versus 4.5% of control patients without IBS.1 The more than 3-fold higher use of antidepressants (odds ratio [OR] = 3.27, 95% confidence interval [CI] = 2.27-4.70) among patients with IBS is not a surprising finding, but the actual use of drugs by IBS patients is little studied despite the high prevalence of IBS, which is estimated to affect 12% of adults in the United States.2 However, a plethora of research reports exist regarding the comorbidity of psychiatric conditions and IBS; a MEDLINE search performed in October 2008 revealed 456 citations for the combination of the search terms “irritable bowel syndrome” and “depression.” The medical literature shows a strong relationship of IBS with anxiety, chronic fatigue syndrome, and fibromyalgia, as well as depression.3,4 The research is sufficiently specific to differentiate a higher frequency of IBS symptoms with panic disorder, generalized anxiety disorder, and major depressive disorder versus social anxiety disorder, specific phobia, and obsessive-compulsive disorder.5

There is considerable discussion regarding the role of serotonin in IBS,6 which suggests that some antidepressants may be more effective than others. Hayee and Forgacs in their clinical review (2007) presented evidence that (a) the diagnosis of IBS is stigmatized by the method of exclusion, leading to an aura of negativity for the patient; (b) IBS does not have a single cause and is associated with a complex of symptoms; (c) the association of IBS with psychiatric disorders begs the question of cause and effect; (d) despite the reported high prevalence of IBS, many more patients may have IBS who do not consult a physician; and (e) among the antidepressant drugs, the tricyclic antidepressants have been studied most often in IBS, with consistently favorable effects and a number needed to treat (NNT) of 3.2 (95% CI=2.1-6.5) compared with an NNT of 2.0 for cognitive behavioral therapy and mixed but generally poor results with the selective serotonin-reuptake inhibitors (SSRIs).7 Unfortunately, in the present study, Faresjö et al. did not record the subtypes of antidepressants (e.g., SSRIs, serotonin–norepinephrine reuptake inhibitors, or tricyclic antidepressants) reported by the respondents in their population survey.

Choice of Antidepressant

Amitriptyline has been shown to be effective in adolescents8 and adults with IBS, even at a low dose (10 mg per day).9 In the meta-analysis performed by Jackson et al. (2000)10 and summarized by Hayee and Forgacs, 7 of 9 clinical trials of tricyclic antidepressants showed a statistically significant effect with an overall mean difference of 0.9 (95% CI=0.6-1.2) compared with placebo.7 Mertz concluded that tricyclic antidepressants are recommended for moderate-to-severe IBS in which pain is prominent or when other therapies have failed.11 Mayer recommends a starting dose of amitriptyline 10 mg at bedtime and gradual dose increases over a period of several weeks to a maximum tolerated dose of not more than 75 mg at bedtime.12 In his expert review, Farthing cited psychological interventions (psychotherapy, short- and long-term hypnotherapy, cognitive behavioral therapy) and antidepressants (low and conventional doses) as effective therapies for IBS, including a therapeutic gain of 33% compared with controls for cognitive behavior therapy.13

Diagnostic Uncertainty

The absence of definitive markers for diagnosis of IBS is not due to a lack of effort. Eriksson et al., for example, studied 80 patients with IBS (30 with diarrhea-predominant IBS [IBS-D], 16 with constipation-predominant IBS [IBS-C], and 34 with alternating IBS [IBS-A]) using 5 psychological and disease-specific scales, a pain score, and biochemical markers (e.g., cortisol, C-peptide).3 These researchers found that IBS-D patients, with a higher proportion of males, had less body awareness, fewer psychological symptoms, a better sense of coherence, and higher C-peptide values compared with IBS-C and IBS-A patients who expressed higher body awareness, more depression and anxiety, and an impaired sense of coherence. For managed care, Hayee and Forgacs concluded that the combination of physical and psychological symptoms with high prevalence in IBS makes the primary...
care setting the logical choice for most IBS patients, with referral to therapists with appropriate psychological skills.

**More Effective and Safe Drug Therapy is Needed**

Because the diagnosis of IBS is often made by exclusion rather than by definitive markers, it is understandable that pharmacotherapy for IBS is as yet imprecise and still evolving. Camilleri and Chang provide an informative perspective on the opportunities and challenges of bringing new pharmacologic entities to market for a condition that has had many end point markers over the past 10-15 years. Mayer (2008) reviewed the drugs and drug classes employed in IBS clinical management, citing only 2 that were approved specifically for IBS: tegaserod (Zelnorm) for IBS-C and alosetron (Lotronex) for IBS-D. Yet a third drug, lubiprostone (Amitiza), also has Food and Drug Administration (FDA) approval specific to IBS-C (in women aged 18 years and older) and is the subject of a recent *JMCP* supplement on management of chronic constipation. The *Medical Letter* consultants concluded in July 2008 that, for a monthly cost of $219.88 for 60 capsules (8 mcg twice daily), lubiprostone “appears to be modestly effective for a small percentage of patients with irritable bowel syndrome with constipation.”

The 8 randomized, controlled trials for tegaserod show that the active drug was 20% more likely to be associated with global symptom relief compared with placebo, but with an NNT of 17. A Cochrane review by Evans et al. (2007) found no effect of tegaserod on pain or discomfort. The side effects that became evident with tegaserod, including adverse cardiovascular events, contributed to the suspension of its marketing in the United States in March 2007; its use was restricted to investigational-drug status in July 2007 for women younger than 55 years who have IBS-C or chronic idiopathic constipation without known cardiovascular problems.

The other promising new chemical entity, alosetron, was approved by the FDA on February 9, 2000, but was withdrawn from the market just 9 months later on November 28, 2000, because of severe adverse effects, including ischemic colitis. Alosetron was reintroduced to the U.S. market on June 7, 2002, under an agreement between the manufacturer and the FDA, restricted to use only in women with severe IBS-D who have failed to respond to conventional therapy and subject to each patient signing a patient-physician agreement. The search for a disease-specific drug for IBS has therefore left 2 of the largest brand-name pharmaceutical manufacturers essentially empty handed. A systematic review that is now 8 years old identified 283 studies of IBS, of which 70 met the inclusion criteria, and concluded that the “strongest evidence for efficacy was shown for smooth-muscle relaxants in patients with abdominal pain as the predominant symptom.” There were 16 studies of smooth-muscle relaxants, such as dicyclomine. The smooth-muscle relaxants have an NNT of 4.5 compared with 3.2 for the tricyclic antidepressants, and both classes are superior to the NNTs for the other 2 classes of drugs: 10.7 for the serotonin-4–receptor agonist tegaserod and 7.6 for the serotonin-3–receptor antagonist alosetron. It is interesting that Faresjo et al. in the present issue of *JMCP* found that this class of drugs (“motility/antispasmodics”) was used by only 1.7% of patients with IBS, which is lower than the use rates for other gastrointestinal medications in IBS patients but dramatically higher than in control patients (OR = 22.06, 95% CI 4.43-119.72).

**Economic Burden of IBS is Potentially Large**

While the point prevalence of IBS is estimated to be 12% of adults in the United States, survey data suggest that IBS may affect as many as 20% of the U.S. population. But because as few as 10% of those with IBS report their symptoms to physicians, the U.S. prevalence rate from administrative claims data ranges from 1% to 6% of the population. Data from the National Ambulatory Medical Care Survey from 1997 to 1999 and the National Center for Health Statistics for 1996 show that IBS affected approximately 1% of the U.S. population, as derived from the primary diagnosis field in medical claims, and accounted for more than 4.4 million physician visits by 2.1 million patients between 1997 and 1999, while Everhart and Renault (1991) estimated that IBS accounted for 3.3 million physician visits per year. More than 20 years ago, Mitchell and Drossman estimated that IBS accounted for 12% of visits to primary care physicians and 28% of visits to gastroenterologists. Talley et al. found that patients with IBS incurred median annual all-cause medical care charges that were 73% higher than healthy controls without IBS ($742 vs. $429 in 1992 dollars). In a systematic review, Inadomi et al. (2003) found the total economic costs of IBS to be $1.56 billion (1998 dollars) in the United States, of which 87% were direct costs and 13% were indirect costs associated with absenteeism from work attributable to IBS symptoms. Hulisz estimated much higher costs of IBS in the United States, including indirect costs associated with lost productivity and adverse effects on quality of life. Until more specific drug therapies for IBS are available, the mainstay of clinical management is the differential diagnosis to rule out conditions, such as colitis or atypical Crohn’s disease, and to present the IBS patient with a model of the disease (e.g., brain-gut disorder) that is plausible, with symptom management of altered bowel habits with either antidiarrheals or laxatives. Physician acknowledgement of the disease may improve the patient-physician relationship and even result in better treatment outcomes. Dietary modification, such as avoidance of suspected dietary triggers and moderation of fat intake, may be effective in some patients; oral fiber supplementation is widely used but without supporting evidence, and there is a significant placebo effect in IBS that may last 3 months or more.
et al. in this issue of JMCP was motivated by the hypothesis that nonspecific (and not recommended) drug therapy, particularly acid-suppressive agents, would be high among patients with IBS compared with controls without IBS. What they found is that 15.0% of IBS patients reported using either prescription (13.3%) or over-the-counter (1.7%) acid-suppressive drugs, which is approximately the same absolute proportion (13.3%) of patients who reported using antidepressants. With 1 in 5 persons potentially affected by IBS, a pharmacologic answer would have an enormous market. On the other hand, Kaptchuk et al. (2008) showed convincingly that IBS is responsive to placebo treatment (sham acupuncture), with significantly greater relief of symptoms, global symptom improvement, and quality-of-life scores when sham acupuncture was combined with augmented patient–provider interaction that included active listening, communication of confidence, and positive expectation of patient response.29 As noted by other reviewers of the research evidence regarding IBS, the quote attributed to Hippocrates may be particularly appropriate for this clinical syndrome: “It is more important to know what sort of person has a disease than to know what sort of disease a person has.”

**REFERENCES**


The hallmark of the Code Talkers’ work was a rapid but exacting translation process. Receiving messages in “a string of seemingly unrelated Navajo words,” each Code Talker first translated the words to English, then used the first letter of each English word to spell out an English message. In addition, both for security purposes and to speed translation, the Code Talkers memorized a dictionary of an astonishing 450 Navajo words representing commonly used military terms; for example, the word “besh-lo” (iron fish) referred to a submarine, “dah-he-tih-hi” (hummingbird) was a fighter plane, and “debeh-li-zine” (black street) indicated a squad. Because of the innate complexity of the Navajo language, the use of multiple Navajo words to represent a single English letter, and the detailed nature of the translation process, the code was both impossible for anyone else to decipher and painstakingly difficult for the Code Talkers themselves. “When we were in the [training] classroom we were drilled and drilled,” one Code Talker recalled in a 2005 interview. “No writing it down. It was all memorized. … At the end of the class you had to hand in every pencil and piece of paper.” Yet, despite the difficulty of the work and the pressures of performing it during combat, the Code Talkers consistently turned in error-free performances. During the first 2 days of the battle of Iwo Jima, 6 Code Talkers worked around the clock to transmit 800 messages, all with 100% accuracy. With some dismay, JMCP editors have recently noted that an increasing number of literature reviews, both in published work and in manuscripts submitted to us, bear little or no resemblance to the careful translations that characterized the heroic cryptographers of WWII. It is common for us to read in a submitted manuscript a statement that “in Disease A, Drug X is widely accepted as more efficacious than Drug Y,” only to find in our research that the source cited for the statement investigated a different disease state, studied only a handful of people, produced a finding that Drug X was not superior to Drug Y, or otherwise did not support the alleged claim.

A case in point is found in examination of the literature published in the years following Soumerai et al’s 1991 often-cited study of the effect of a medication coverage limit on a sample of chronically ill elderly Medicaid enrollees in New Hampshire. A comparison of the original study report with descriptions of the study that were provided in later manuscripts provides a revealing and at times disturbing look at the uses—and abuses—of medical literature applied in the service of making a point. This editorial reviews a sample of those descriptions and suggests a direction for the future.

The Original Study: Medicaid Prescription Drug Restrictions and Use of Hospital and Nursing Home Services

Soumerai et al’s 1991 study assessed the relationship between a prescription drug “cap,” a limit of 3 filled prescriptions per month per Medicaid recipient, and admissions to nursing homes and inpatient hospitals. The cap had been implemented in the New Hampshire Medicaid program in September 1981 and replaced 11 months later, in August 1982, with a $1 prescription drug copayment. The study authors used a quasi-experimental, time series with comparison group design to assess outcomes for a subset of Medicaid enrollees (n = 411) who met clinical and demographic criteria indicating older age and chronic illness (Table 1). The comparison group (n = 1,375), which was drawn from the New Jersey Medicaid population, met the same inclusion criteria but had not been subject to any prescription drug cost-sharing or coverage limitations.

Outcomes, including medication use and admissions to inpatient hospitals and nursing homes, were measured during a 5-month pre-implementation period, the 11-month cap period, and for 11 months after the replacement of the cap with the copayment. Measured in “standardized monthly doses” (SMDs) per patient per month (PPPM), defined as “the median number of milligrams of active ingredient per month received by all the patients who filed a claim for each study drug,” medication use rates for the New Hampshire cohort declined from a pre-implementation rate of 2.8 SMDs PPPM to a cap period rate of 1.9 SMDs PPPM. Time-series analysis indicated that the change represented a 35% drop. By the end of the 11-month cap period, nursing home admission rates were 10.6% and 6.6% for the New Hampshire and New Jersey cohorts, respectively. The relative risk...
(RR) of nursing home admission for the sample overall was 1.8 (95% confidence interval [CI] = 1.2-2.6).

The results most frequently reported for the study are derived from a subsample of study patients (48% of 411 in New Hampshire and 55% of 1,375 in New Jersey) who had at least 8 claims per year for at least 3 chronic medication classes (including the “core” therapeutic classes used in the sampling process plus 21 therapeutic classes for treatment of cardiovascular disease, diabetes, psychiatric disorders, pain, and other conditions). For this subsample, nursing home admission rates were 14.4% for New Hampshire and 6.2% for New Jersey; the reported RR of nursing home admission for New Hampshire was 2.2 (95% CI = 1.2-4.1).5 However, among those who did not meet the subsample criteria, the relationship between the cap and nursing home admission was not statistically significant.7 Moreover, even among those who did meet the subsample criteria, rates of hospital admission for New Hampshire and New Jersey Medicaid recipients during the cap period did not significantly differ (RR = 1.2, 95% CI = 0.8-1.6).5 Attributing their findings to either “declining health” because of “loss of medications” or “financial reasons” arising from additional medication expense, Soumerai et al. concluded that their findings “raise questions about the clinical and economic wisdom” of “limits on drug reimbursement” in state Medicaid programs.5

Shortly after the study’s publication, a commentary by Schulz and Lewis raised several concerns about its conclusions, calling them “tentative at best.”7 One of the most compelling of Schulz and Lewis’s stated reasons for skepticism about the study’s findings was the lack of relationship between the cap and hospital admission. If the cap had resulted in deteriorating health status, Schulz and Lewis pointed out, one would logically expect both hospital and nursing home use to be affected. Schulz and Lewis also appropriately questioned the logic of Soumerai et al.’s alternative explanation for their findings—that community-dwelling elderly had entered nursing homes in order to avoid paying out-of-pocket for medications. Schulz and Lewis concluded with the important prediction that, although the sampling criteria used by Soumerai et al. were so restrictive that their results were “not representative of a sizeable group of the population,” the “appeal of the authors’ conclusions to some [health care] constituencies” would raise “the danger that broad generalizations will be voiced, and policy decisions may be influenced, by a study whose conclusions should be interpreted cautiously.”7


Schulz and Lewis’s expectation that Soumerai et al.’s findings would have broad appeal was certainly realized in the years following the study’s publication. To date, more than 300 published papers have cited the work.8 Consistent with Schulz and Lewis’s concerns, examination of a convenience sample of these publications reveals numerous serious errors in describing the study’s results (Table 2).9-24 The most common and serious error was attributing inpatient hospitalizations to the cap although Soumerai et al. found no significant relationship between the cap and hospital admission rates.9,11-13,19,21,23

Additional errors occurred when describing the cap itself, which was commonly represented as a formulary.12,16,19-21 Similarly, one description of the paper attributed negative outcomes to copayments despite Soumerai et al.’s finding that the risk of nursing home admission returned to its baseline (pre-cap) level when the cap was replaced by a $1 copayment.5,7 Notably, some discussions of the work cited outcomes that were not even studied by Soumerai et al.; these included changes in physician practice patterns, prescribing rates, emergency room use, and even mortality.12,14,18,22,24

More recently, an erroneous description of the study appeared in a 2007 publication (not shown in Table 2), which stated that the cap “was found to be associated with increased nursing home admissions 10 years after implementation.”25 The statement implied that the risk of nursing home admission continued to be elevated 10 years after cap implementation; in fact, the original study report indicated that the nursing home admission rate reverted to pre-cap levels upon replacement of the 3-prescription cap with the $1 copayment.

As Schulz and Lewis predicted in 1992, a particularly common error, appearing in numerous publications not shown in the table, was failing to describe the highly selective clinical characteristics of Soumerai et al.’s subsample.26-35 Omission of the subsampling criterion of at least 8 claims per year for at least 3 chronic medication classes is an especially important mistake because among those with less regular use (i.e., either less than 3 chronic medication classes or less regular use of 3 or more chronic classes), the risk of nursing home admission was not significantly related to the cap.5 Thus, decision-makers relying on these publications for information would be given the erroneous impression that the increased nursing home risk applied only to all Medicaid enrollees, to all elderly Medicaid enrollees, or to all elderly Medicaid enrollees with chronic disease. Such a misimpression limits the opportunity

### Table 1 Sample Selection Criteria for Soumerai et al. Study of Medicaid Drug Payment Cap5

- Aged 60 years or older
- White race
- No nursing home admissions during the 6 pre-implementation months
- Filled a mean of 3 or more prescriptions per month (total of 36 claims) for any medications during baseline pre-implementation year
- At least 1 prescription per quarter for any medications during baseline year
- ”Regular use” (at least 8 claims per year) of at least 1 ”core” medication, defined as a drug in any of the following therapeutic classes—antianginal drugs, loop diuretics, antiarrhythmic agents, bronchodilators, inhaled steroids, insulin, anticoagulants, and anticonvulsants—during baseline year

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## Table 2  Soumerai et al. Study of Medicaid Payment Cap: Inaccurate Descriptions—1991-2001

<table>
<thead>
<tr>
<th>Study (First Author and Year)</th>
<th>Were key details about the sample reported?</th>
<th>Description of Findings</th>
<th>Problem(s) in Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Income&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Elderly</td>
<td>Chronic Medication Use&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Balkrishnan, 1998&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Billings, 1996&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blustein, 1998&lt;sup&gt;11&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Bukstein, 1997&lt;sup&gt;12&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Elliott, 1996&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Fraser, 1996&lt;sup&gt;14&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Hennessey, 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Horn, 1996&lt;sup&gt;16&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Johnstone, 1993&lt;sup&gt;17&lt;/sup&gt;</td>
<td>No</td>
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<tr>
<td>Lipton, 1993&lt;sup&gt;18&lt;/sup&gt;</td>
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<td>Lo, 2000&lt;sup&gt;19&lt;/sup&gt;</td>
<td>No</td>
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<tr>
<td>Miller, 2000&lt;sup&gt;20&lt;/sup&gt;</td>
<td>No</td>
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<td>No</td>
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</table>
of the decision-maker to target benefit design decisions to those unlikely to be harmed by them. In that regard, it is notable that the subsample (n=approximately 197 [48% of 411] enrollees) in which the nursing home admission rate was elevated represented less than 2% of the 10,734 continuously enrolled New Hampshire Medicaid recipients affected by the cap.6

We Can Do Better: Literature Review That Is Both Accurate and Concise

A suggested checklist for literature review descriptions is shown in Table 3. Although not intended to be comprehensive, the checklist presents the core basic elements that should be included in a description of previously published research. As the examples demonstrate, descriptions do not have to be lengthy, and it rarely takes many more words to describe a study adequately than to describe it inadequately. The key to informative literature review is specificity.

Descriptions should be sufficiently complete to give managed care decision-makers a sense of the degree to which the study group represents the population about which decisions must be made. For example, a study sample consisting primarily of males treated at Department of Veterans Affairs (VA) clinics for congestive heart failure would appear to have limited applicability to a commercially insured population in a service industry such as banking that employs primarily young females. Descriptions should also indicate absolute rates rather than relying solely on relative rates. For example, the phrase “a 100% increase in risk” could represent a change either from 1% to 2% or from 25% to 50%, yet these ranges clearly have very different clinical and economic implications. Readers should also be given the temporal context for a study within clinically meaningful time frames; for example, they should be told if a study of routine clinical practice was conducted before or after the promulgation of key clinical guidelines or the development of an important technique that changed medical practice patterns.

Learning From the Navajo Code Talkers

Although pharmacoeconomic literature review is unlikely ever to approach the level of importance of the work of the Code Talkers, providing accurate information to managed care decision-makers is becoming increasingly critical as debate over health care policy proposals becomes progressively more intense. Consider what the outcome of WWII might have been, had the Navajo Code Talkers approached their work with the same complacency that characterizes too much of medical research literature review today. If those of us who promulgate information about health care evidence can achieve even a fraction of the dedication, attention to detail, and accuracy that

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**Table 2** Soumerai et al. Study of Medicaid Payment Cap: Inaccurate Descriptions—1991-2001

<table>
<thead>
<tr>
<th>Study (First Author and Year)</th>
<th>Low-Incomea</th>
<th>Elderly</th>
<th>Chronic Medication Useb</th>
<th>Description of Findings</th>
<th>Problem(s) in Description</th>
</tr>
</thead>
</table>
| Morreim, 199821             | No          | No      | No                      | “Tightly constrained drug formularies may save short-term pharmacy costs, but they can raise rates of hospitalization and emergency room use because some patients experience greater side-effects and adherence problems from older, cheaper, or generic drugs that are not quite equivalent to their newer counterparts.” | • The New Hampshire cap was not a formulary. 
• Relationship between the cap and hospitalization risk was not statistically significant. |
| Powe, 199322                | No          | No      | No                      | “there have been few empirical studies which have provided strong evidence that federal payment policies can directly influence medical practice.” | • Soumerai et al. did not study medical practice. |
| Rosenberg, 199423           | Yes         | No      | No                      | The cap “put Medicaid recipients at much higher risk of hospitalization (50% higher than the control group).” | • Relationship between the cap and hospitalization risk was not statistically significant. 
• The RR was 1.2, which would have indicated a 20% increase if statistically significant. |
| Sumner, 199324              | Yes         | Yes     | Yes                     | The cap “was associated with an increased nursing home admission rate and an increased mortality rate…” | • Soumerai et al. did not measure mortality rate. |

*aIncludes explanations that the sample consisted of Medicaid enrollees. 
bFull disclosure would include mention of the subsample criterion of at least 8 claims for at least 3 chronic medications. No study shown in the table mentioned that criterion. A “Yes” in the table indicates mention of chronic disease. 
CI=confidence interval; RR=relative risk.
TABLE 3

<table>
<thead>
<tr>
<th>Principle to Disclose</th>
<th>Description Should Include</th>
<th>Example of Sufficient Descriptive Phrasea</th>
<th>Example of Insufficient Descriptive Phrasea</th>
</tr>
</thead>
</table>
| Who                   | 1. Demographic and clinical characteristics  
2. Key sample selection criteria                                                    | • Male veterans receiving treatment at VA Clinics for congestive heart failure  
• Used 2 or more medications to treat cardiac disease during a 6-month pre-intervention period | • Veterans with serious cardiac disease  
• Patients using chronic medications |
| What                  | 3. Specific outcomes measured  
4. Time period for measurement  
5. Absolute findings, not just relative ratios  
6. Number of cases                                                      | • Hospitalization rate was 5.2% in the comparison group and 2.2% in the intervention group (OR 2.44; 95% CI=1.24-3.64) in 6 months of follow-up | • Intervention group patients were 58% less likely to be hospitalized.  
• The intervention significantly reduced hospitalization risk |
| When and Where         | 7. Time period for conduct of study, especially if standards of care have changed over time  
8. Type of setting  
9. Diagnoses and ICD-9-CM codes, especially for claims database studies if comparing to a different claims database study | • Patients receiving at least 1 office visit for hypercholesterolemia during 2003, 1 year prior to the publication of ATP-III guidelines in April 2004  
• Patients receiving care for schizophrenia at a clinic that serves primarily Medicaid and working poor patients  
• Patients with a primary diagnosis of unspecified chest pain (ICD-9-CM code of 786.50 or 786.59) for an emergency room visit (revenue codes 450-459) during 2005 | • Patients diagnosed with hypercholesterolemia  
• Patients who are low-income and mentally ill  
• Patients receiving care from an emergency room |

a Examples are hypothetical.

ATP-III=Adult Treatment Panel III; CI=confidence interval; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; OR=odds ratio; RR=relative risk; VA=Department of Veterans Affairs.

Accuracy in Pharmacoeconomic Literature Review: Lessons Learned From the Navajo Code Talkers

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DISCLOSURES

The author reports no conflicts of interest related to the subjects or products discussed in this article.

REFERENCES


