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he word “carousel” is derived from the words *garosello* (Italian) and *carosella* (Spanish), both of which mean “little war.” Carousel was a game played among Arabian and Turkish horsemen as preparation for combat during the 12th century. Clay balls filled with scented water were tossed back and forth between the riders. The losers were those who missed a catch—when the ball broke upon impact, they smelled of perfume as a consequence.

In the late 15th century, the French developed their own version of carousel called *carrousel* and transformed it into a grand festival of pageantry and horsemanship. One of the highlights of the event was a ring-spearin competition in which horsemen used their lances to spear small rings suspended from a post while riding at a gallop. To practice for this contest, someone built a device with wooden horses hanging from beams attached to a center pole; it was twirled around by a horse or mule. Young men rode these carved figures and attempted to spear golden rings dangling along the perimeter of the apparatus. Thus, the carousel as we know it was born.

Eventually, local craftsmen produced these relatively simple mechanisms for the general public. In 1870, an English engineer named Frederick Savage adapted the steam engine and attached it to machinery that rotated the platform, thereby increasing the feasible size of the carousel, also known as the merry-go-round. Machines could now support up to 5 concentric rows of wooden horses. In addition to horses, many early carousels were populated with animals such as tigers, lions, giraffes, camels, goats, dogs, and rabbits.

During the late 19th century, the popularity of carousels reached new heights in the United States and Europe, and American carousel manufacturers were eager to hire skilled European artisans. Some of these men had experience in the carousel industry, but many of them had honed their carving skills by making decorative items for churches and synagogues. By the turn of the century, several American carousel styles had emerged. The Philadelphia style was associated with carvers Gustav Dentzel and Daniel Muller, the Coney Island style with Charles Looff and Marcus Charles Illions, and the Country Fair style with Allan Herschell and Charles Wallace Parker.

Craftsmen employed at the Philadelphia Toboggan Company in Hatfield, Pennsylvania, produced realistic carousel figures that characterized the Philadelphia style. Frank Caretta, an Old World woodcarver from Milan, Italy, joined the company in 1912 and soon became its head carver. He was a former furniture maker who found his niche creating lifelike carousel horses with whimsical expressions. Caretta painted the animals with bold colors and applied gold and aluminum leaf, particularly on the armored lead horses that bore the Philadelphia Toboggan Company’s initials “PTC.” According to the book *Painted Ponies: American Carousel Art* by William Manns and Marianne Stevens, "Caretta twice won first prizes for carving at National Association of Amusement Parks conventions. In 1928, he won with a dappled charger crowned with a massive tossed mane. A medieval stallion with ornate trappings earned him another award in 1929." This award was for the *PTC Silver Anniversary Carousel Horse*, an outside-row stander made to commemorate the Philadelphia Toboggan Company’s silver anniversary in 1928. It was a one-of-a-kind display figure that showcased Caretta’s extraordinary woodcarving skills. From the delicate flowers on the golden armored headdress to the lion’s head clutching the flowing orange saddle blanket, no detail was overlooked. He even embellished the steel with paste jewels. Caretta also followed the tradition of adorning the side of the carousel horse that faces the audience (the so-called romance side). In the United States and most of Europe, this is the right side of the figure because the carousels in these countries rotate counterclockwise. But in the United Kingdom, the carousel animals are heavily carved on the left side because their “roundabouts” turn clockwise.

Some carousels offer riders a chance to “grab the brass ring,” a tribute to the original French carousels. After the machine is up to full speed, a large metal arm on the outer edge is lowered down within reach—people riding on the outside row can try to grab the brass ring from the arm’s end, good for one free ride.

1925 was the last year of the “golden age of the carousel,” which had begun in 1905. The Philadelphia Toboggan Company ceased the production of carousels in the early 1930s, but it still operates today as Philadelphia Toboggan Coasters, Inc., the world’s leading producer of cars for wooden roller coasters. Luckily, some of the antique merry-go-rounds have survived—those magical machines filled with brightly colored wooden animals, mirrors, lights, and band-organ music. To find one near you, visit the National Carousel Association’s Web site at nca-usa.org. *Painted Ponies* and other books about carousels can be found on Zon International Publishing’s Web site at zonbooks.com.

Sheila Macho
Cover Editor
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**ABSTRACT**

**BACKGROUND:** Breast cancer is one of the most common forms of cancer in the United States, with approximately 10% of newly diagnosed patients presenting with metastatic disease. Limited therapy options make the successful treatment of metastatic breast cancer (MBC) difficult. Current treatment options include drugs belonging to the classes of anthracyclines and taxanes as well as the drug capecitabine. Resistance to these classes of drugs is often acquired, thus highlighting the need for newer agents capable of managing treatment resistant disease. Ixabepilone is an antineoplastic agent from the epothilone class that was FDA-approved in October 2007 for the treatment of metastatic or locally advanced breast cancer. The FDA-approved indications for ixabepilone specify (a) use of ixabepilone in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer after (resistance to) treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated; and (b) ixabepilone as a monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to an anthracycline, a taxane, and capecitabine.

**OBJECTIVES:** To estimate the 3-year projected impact on the annual pharmacy budget for a hypothetical 1 million-member commercial plan that introduces and reimburses ixabepilone therapy for its FDA-approved indications: either as a monotherapy for patients pretreated with combined anthracyclines, taxanes, and capecitabine (ATC-p) or in combination with capecitabine for patients pretreated with anthracyclines and taxanes (AT-p).

**METHODS:** U.S. prevalence and treatment data for MBC patients were obtained from published and nonpublished sources. The MBC population was stratified into AT-p and ATC-p populations. These 2 groups comprised the assumed study population. The model considered 2 scenarios—without (pre) and with (post) ixabepilone, either as monotherapy for ATC-p or combination therapy with capecitabine for AT-p patients. Market share data for chemotherapeutic treatment options for MBC pre-ixabepilone and in the first year post-ixabepilone were obtained from nonpublished, proprietary, real-world drug utilization data collected by IntrinsiQ LLC (Waltham, MA), for 2007 and 2008, respectively. Market share for the second and third years post-ixabepilone were forecasted by the study authors based on IntrinsiQ data collected from January 2008 to January 2009 and the observed switching patterns in the 2007 and 2008 IntrinsiQ data.

Drug costs were based on First DataBank Inc. Wholesale Acquisition Cost (accessed March 2009). The results for each indication were analyzed individually and summed to reflect the total impact of ixabepilone. Results were also considered on a per member per month (PMPM) basis to examine the relative impact on the plan. Sensitivity of the results to model assumptions was tested using univariate sensitivity analyses on the prevalence of AT-p and ATC-p, the price of ixabepilone, the price of comparator medications, and the ixabepilone market uptake. A key assumption was that ixabepilone would be used only in accordance with its current labeled indications.

**RESULTS:** In a health plan population of 1 million members, the estimated number of female patients aged 20 years or older with recurrent MBC and previous treatment with either AT or ATC was 15 over the 3-year time horizon used in this budget impact model. For AT-p patients, the estimated incremental cost PMPM was $0.002 for each of the 3 years. The estimated incremental cost PMPM for the ATC-p population was $0.003 for year 1 and $0.004 for both year 2 and year 3. In sensitivity analyses, the PMPM impact varied between -$0.01 and $0.02 over the 3-year period. The model was most sensitive to the cost of ixabepilone.

**CONCLUSION:** Given the poor prognosis and limited number of treatment options for patients with MBC, the need for widespread coverage of ixabepilone in accordance with FDA-approved indications can clearly be established. Assuming that ixabepilone is used only for its currently labeled indications, both the number of patients eligible for ixabepilone treatment and the expected budget impact of covering ixabepilone for this group of patients are relatively small.

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In the United States, breast cancer is the second most common form of cancer and the second-leading cause of cancer deaths among women. In 2009, an estimated 192,370 American women will be diagnosed with this disease. While the majority of women will be diagnosed during earlier stages of the disease when curative approaches are possible, approximately 10% of newly diagnosed patients have locally advanced or metastatic disease. Once metastases are detected, the median survival time is approximately 18-24 months. Recent estimates show that the 5-year survival rate for women with metastatic breast cancer (MBC) is 27%. In 2006, it was estimated that close to 50,000 women across North America died from MBC, and that more than 400,000 women worldwide will die annually of this disease. During the advanced stages of MBC, treatments are often palliative in nature rather than curative.

The current standard of care for systemic breast cancer treatment involves therapy with anthracyclines and/or taxanes. While response rates of 30% or more are routinely achieved in previously untreated patients, response rates decrease significantly in patients previously exposed to chemotherapy. With the increased use of anthracyclines and taxanes, clinicians now face the challenge of managing disease progression, or recurrence, in patients who are anthracycline and taxane resistant. Patients with MBC who have progressed after treatment with anthracyclines and taxanes have limited treatment choices, and many of these options have low response rates. In these patients, capcitabine treatment has been shown to achieve response rates ranging from 9% to 14% in phase III studies, while other agents have shown to have less efficacy. These relatively poor response rates highlight the need for newer agents that can be used to treat individuals whose disease has progressed after treatment with anthracyclines and/or taxanes has failed.

Epothilones are a new class of nontaxane, tubulin stabilizing agents possessing potent cytotoxic activity and reduced susceptibility to a variety of multidrug resistance mechanisms that lead to taxane resistance. Ixabepilone (BMS-247550) is a semisynthetic analog of the natural product epothilone B. It was designed to have improved pharmacological properties, while retaining the activity and resistance profile of the natural compound. Ixabepilone has demonstrated activity in metastatic and locally advanced breast cancer, both as a monotherapy and when combined with capcitabine. In the pivotal phase III clinical trial, adding ixabepilone to capcitabine prolonged progression-free survival (median 5.8 months vs. 4.2 months for capcitabine alone, HR for progression=0.75, 95% CI=0.64-0.88, P<0.001). Although results from clinical trials are able to demonstrate the clinical efficacy of ixabepilone, in health care environments with limited financial resources, new therapies such as ixabepilone are also closely scrutinized for the potential impact they may have upon pharmacy budgets.

The objective of this study was to model the annual direct pharmacy cost of introducing ixabepilone as a treatment option for patients with MBC. Specifically, we considered the impact upon a hypothetical health plan with 1 million members over a 3-year time horizon, where ixabepilone therapy was used as a monotherapy for patients previously treated with the combination of anthracyclines, taxanes, and capcitabine or ixabepilone in combination with capcitabine for patients previously treated with anthracyclines and taxanes. Only ixabepilone use strictly in accordance with its currently labeled indications was considered.

Methods

Model Structure and Calculations

The model analysis was conducted according to the budget impact analysis guidelines promulgated in 2007 by the International Society for PharmacoEconomics and Outcomes Research (ISPOR). The target study population for ixabepilone treatment is female MBC patients who are aged 20 years or older and are anthracycline and taxane pretreated (AT-p) or anthracycline, taxane, and capcitabine pretreated (ATC-p). For the hypothetical plan membership, the population percentages and respective patient numbers considered in the analysis are shown in Table 1. Breast cancer prevalence data were drawn from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1975-2005 for U.S. prevalence counts (invasive cancers only), January 2005, by age at prevalence. Specifically, the number of females aged 20 years or older with breast cancer was used to calculate the prevalence, assuming the U.S. population to be approximately 300,000,000 individuals. The proportion of female breast cancer patients with MBC was derived from U.S. SEER data using CancerMPact Comprehensive Cancer Epidemiology data purchased from The MatsonJack Group, Inc. (St. Louis, MO). The AT-p and ATC-p prevalence rates were taken from 2007 market research data purchased from IntrinsiQ (IntrinsiQ LLC Waltham, MA). IntrinsiQ data are derived from the electronic collection of patient-level drug utilization data from 36 states, which are updated on a monthly basis.

The populations identified to receive therapy were modeled according to market share distributions in the pre-ixabepilone scenario (market without ixabepilone) and the post-ixabepilone market (with ixabepilone). In the pre-ixabepilone scenario, it was assumed that ixabepilone is not available for use in the patient population, whereas the post-ixabepilone scenario assumed that ixabepilone was listed on the formulary as a treatment option for treatment-resistant MBC only. For each of the 3 years modeled in the analysis, a cross-sectional assessment of a payer budget was taken, where the pre-ixabepilone market was assumed to be constant. Both the pre- and first-year post-ixabepilone scenarios were derived from proprietary unpublished data that were purchased from IntrinsiQ by the study authors for use in this model. Real-world drug utilization data for 2007 were used for the pre-ixabepilone scenario, while 2008 utilization data were...
used for the first year post-ixabepilone (year 1). Both data sets were collected by IntrinsiQ.19

Market shares for the second and third years post-ixabepilone (year 2, year 3) were then forecasted by the study authors using the drug utilization data collected by IntrinsiQ from January 2008 to January 2009, combined with the market uptakes and switching patterns observed in the 2007 to 2008 IntrinsiQ drug utilization data. Because ISPOR guidelines do not recommend a method for forecasting the budget impact of off-label use, it was assumed that use of ixabepilone would be limited to its currently labeled indications only.

To project the ixabepilone market uptake trends for year 2 and year 3, a trend analysis was conducted using the 13-month (January 2008 through January 2009) IntrinsiQ market research data as the basis for the analysis. To confirm the results of the forecasting analysis, a 3-month moving average approach was applied starting with the first 3 months of January 2008 and forecasting through January 2009 to project market share values for year 2 and year 3. Similar results were obtained using both methods. The remaining market share not receiving ixabepilone therapy was then allocated proportionally based on the pre-ixabepilone distribution.

To establish the annual pharmacy costs for each treatment, the average annual costs were calculated based on the average course of treatment. Drug costs were based on wholesale acquisition cost (FirstDataBank Inc., San Bruno, CA; accessed March 2009).20 The annual pharmacy costs were calculated using the recommended dosing schedules, based on the respective product information sheets.21-35 The median cycle lengths of all drug therapies were based on opinions provided by physicians employed or retained by the study sponsor. Details of these calculations are available upon request. Rebates and copayments were not included in the analysis. The projected pharmacy costs for each treatment were then applied to the pre- and post-ixabepilone market shares to calculate the estimated incremental budget impact of adding ixabepilone to the hypothetical formulary for years 1, 2, and 3 for the AT-p and ATC-p markets, respectively. All therapies considered within the model were assumed to have similar clinical efficacy and side effect profiles.

The results for each indication, AT-p and ATC-p, were summed to estimate the incremental budget impact for all patients with treatment-resistant MBC. Since the formula is arbitrarily chosen to represent 1 million members, the results are presented in a standardized format of incremental impact per member per month (PMPM).

Model assumptions were tested using multiple univariate sensitivity analyses. The prevalence of AT-p and ATC-p, the price of ixabepilone, the price of comparator medications, and ixabepilone market uptake were all varied by +/- 50% from the base case. A larger +/- 50% range was chosen, in contrast to the more typical ranges of +/- 20% or 25%, in order to better account for any reasonable variations of the assumptions used in the model. An increased mortality rate of 5% for each year and rates of 80% or 90% drug compliance for ixabepilone were also included in the sensitivity analyses. Two separate 4-way sensitivity analyses were also conducted to assess best-case and worst-case scenarios for ixabepilone. For the best-case analysis, a 50% decrease in the prevalence rate, a 50% decrease in the ixabepilone market uptake rate, a 50% increase in the cost of other drugs, and a 50% decrease in the ixabepilone price were assumed. For the worst-case analysis, a 50% increase in the prevalence rate, a 50% increase in theixabepilone market uptake, a 50% decrease in the cost of other drugs, and a 50% increase in the ixabepilone price were assumed.

An Excel spreadsheet-based model using Visual Basic for Applications (Microsoft Corporation, Redmond, WA) was created for all modeling calculations and simulations. The resulting estimates were reported in 2009 U.S. dollars for years 1, 2, and 3.
### TABLE 2  Market Share Scenario Inputs for AT-p Population for Years 1 Through 3

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<td># Patients</td>
<td>% Patients</td>
<td># to IXA</td>
<td>% Patients</td>
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<td>C2-C4</td>
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<td>C2-C6</td>
<td>C8x97</td>
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<td>1.92</td>
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<td>Paclitaxel</td>
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<td>0.11</td>
<td>0.11</td>
<td>9.89</td>
<td>9.58</td>
</tr>
<tr>
<td>Paclitaxel, albumin bound</td>
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<td>0.11</td>
<td>0.11</td>
<td>9.89</td>
<td>9.58</td>
</tr>
<tr>
<td>Trastuzumab</td>
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<td>0.02</td>
<td>1.98</td>
<td>1.92</td>
</tr>
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<td>n/a</td>
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</table>

*Numbers shown in the table may not exactly multiply or sum to totals shown because of rounding.

Market share analysis performed by study authors using proprietary nonpublished data from IntrinsiQ LLC (Waltham, MA) for 2007.

Market share analysis performed by study authors using proprietary nonpublished data from IntrinsiQ LLC (Waltham, MA) for 2008.

Market share analysis performed by study authors using proprietary nonpublished data from IntrinsiQ LLC (Waltham, MA) for January 2008 to January 2009 as a basis for forecasting.

Other = tamoxifen, anastrozole, goserelin.

AT-p = pretreated with anthracyclines and taxanes; IXA = ixabepilone; MBC = metastatic breast cancer.

### Results

Tables 2 and 3 show the market share and corresponding population distributions for both the pre-ixabepilone scenario and post-ixabepilone scenarios for years 1-3 for the AT-p and ATC-p populations, respectively. The total annual drug costs for the pre-ixabepilone scenario, the post-ixabepilone scenarios, and the incremental budget impact for years 1 through 3 are shown in Tables 4 and 5 for the AT-p and ATC-p treated populations, respectively.

Based upon IntrinsiQ market research data for ixabepilone, January 2008 to January 2009, 2.09% of all AT-p MBC patients were assigned to receive ixabepilone in combination with capecitabine following market introduction in year 1 (Table 2). Based upon market projections from this data, it was determined that 2.03% and 2.00% would receive ixabepilone combination therapy for years 2 and 3, respectively. Based on these assumptions, it was estimated that 2 AT-p patients would be eligible for ixabepilone therapy for each of the 3 years. The estimated incremental budget impact amounts for AT-p patients were calculated to be $23,103, $22,287, and $21,943 for years 1, 2, and 3, respectively (Table 4). When the estimated total budget was shared across all plan members, the incremental cost PMPM was $0.002 for each of the 3 years.

For the ATC-p population, an estimated 148 patients were eligible for ixabepilone therapy, of whom 12 patients in year 1 (8.39%) and 13 patients in each of years 2 and 3 (8.64% and 8.61%, respectively) were projected to receive ixabepilone therapy (Table 3). Based on these drug cost estimates for an ATC-p population receiving ixabepilone, the incremental budget impact amounts were $41,428 in year 1, $47,236 in year 2, and $47,695 in year 3 (Table 5). When these costs were shared across the membership, the costs PMPM were $0.003 for year 1 and $0.004 for years 2 and 3 (Table 5).

The overall total budget impact amounts of introducing ixabepilone, aggregated for both the AT-p and ATC-p patient

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Budget Impact Analysis of Ixabepilone Used According to FDA-Approved Labeling in Treatment-Resistant Metastatic Breast Cancer
option for some patients. A budget impact model was developed to estimate the impact of introducing ixabepilone monotherapy or ixabepilone and capecitabine combination therapy as a treatment option for female MBC patients previously treated with other therapies in a commercial plan with a 1 million-member population.

In this model, it was estimated that the budgetary impact of adding ixabepilone to a health plan strictly in accordance with its FDA-labeled indications would be minimal. This minimal pharmacy budget impact is mostly likely attributable to the fact that the estimated size of the population to receive ixabepilone therapy, a total of 15 patients out of a hypothetical plan membership of 1 million enrollees, is relatively small. The sensitivity analysis tested various assumptions, including the estimated size of the population that would receive ixabepilone in accordance with its labeled indications and found drug price to be one of the primary driving factors for the budget impact variance.

The PMPM cost estimated in this model is relatively minor and is less than the PMPM costs of other chemotherapy agents found in the literature. For example, in an analysis of administrative pharmacy claims for an insured health plan of approximately 500,000 members, 2 newly approved medications at the time of the analyses, lenalidomide and sunitinib, were found to have PMPM costs of $0.03 and $0.05, respectively. Two of the most costly medications in the analysis were erlotinib and imatinib mesylate, with PMPM costs of $0.09 and $0.12. The PMPM cost estimated for ixabepilone in the present model for any year was $0.006 for years 2 and 3 for

![Figure 1: Summary of Sensitivity Analyses on Incremental PMPM Cost](image-url)

*AT-p = pretreated with anthracyclines and taxanes; ATC-p = pretreated with anthracyclines, taxanes, and capecitabine; PMPM = per member per month.*

populations, were estimated at $64,531, $69,523, and $69,638 for years 1, 2, and 3, respectively. The aggregated AT-p and ATC-p population PMPM costs were determined to be $0.005 for year 1 and $0.006 for years 2 and 3.

### Sensitivity Analyses

The results of multiple 1-way sensitivity analyses to test the uncertainty surrounding model inputs showed that the incremental PMPM costs ranged from –$0.01 to $0.02 for each of the 3 years. Increasing the mortality rate to 5% for each year of the model time horizon or assuming 80% or 90% drug compliance for ixabepilone also had little impact upon the incremental PMPM cost. The sensitivity analysis also showed that the model was most sensitive to the cost of ixabepilone and the cost of the other MBC treatment options (Figure 1). The results of the best-case and worst-case sensitivity analyses demonstrated that PMPM costs would vary between $–0.01 and $0.02. Overall, all scenarios tested produced little change to the PMPM costs.

### Discussion

The prognosis for MBC is generally poor. Currently, patients with MBC have few viable efficacious treatment options after resistance to anthracycline, taxane, and/or capecitabine. The treatment options that are available to these patients are often viewed as primarily palliative rather than curative. Moreover, the significant amount of off-label drug use that occurs when treating these patients suggests a strong unmet medical need for new MBC therapies. Ixabepilone offers a new and effective treatment option for some patients. A budget impact model was developed to estimate the impact of introducing ixabepilone monotherapy or ixabepilone and capecitabine combination therapy as a treatment option for female MBC patients previously treated with other therapies in a commercial plan with a 1 million-member population.

In this model, it was estimated that the budgetary impact of adding ixabepilone to a health plan strictly in accordance with its FDA-labeled indications would be minimal. This minimal pharmacy budget impact is mostly likely attributable to the fact that the estimated size of the population to receive ixabepilone therapy, a total of 15 patients out of a hypothetical plan membership of 1 million enrollees, is relatively small. The sensitivity analysis tested various assumptions, including the estimated size of the population that would receive ixabepilone in accordance with its labeled indications and found drug price to be one of the primary driving factors for the budget impact variance.

The PMPM cost estimated in this model is relatively minor and is less than the PMPM costs of other chemotherapy agents found in the literature. For example, in an analysis of administrative pharmacy claims for an insured health plan of approximately 500,000 members, 2 newly approved medications at the time of the analyses, lenalidomide and sunitinib, were found to have PMPM costs of $0.03 and $0.05, respectively. Two of the most costly medications in the analysis were erlotinib and imatinib mesylate, with PMPM costs of $0.09 and $0.12. The PMPM cost estimated for ixabepilone in the present model for any year was $0.006 for years 2 and 3 for
Budget Impact Analysis of Ixabepilone Used According to FDA-Approved Labeling in Treatment-Resistant Metastatic Breast Cancer

**TABLE 3** Market Share Scenario Inputs for ATC-p Population for Years 1 Through 3

<table>
<thead>
<tr>
<th></th>
<th>Pre-IXA</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Patients</td>
<td>% to IXA</td>
<td>% Patients</td>
<td>% Patients</td>
</tr>
<tr>
<td>Column Number (C)</td>
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<td></td>
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<td>C4x148</td>
<td>C2-C4</td>
<td>C6x148</td>
</tr>
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<td>Female ATC-p MBC patients</td>
<td>148</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Capcitabine</td>
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<td>29.63</td>
<td>1.34</td>
<td>1.98</td>
</tr>
<tr>
<td>Carboplatin</td>
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<td>7.41</td>
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<td>0.38</td>
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<td>0.23</td>
</tr>
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<td>Vinorelbine</td>
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<td>1.98</td>
<td>2.94</td>
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<td>148.13</td>
<td>8.39</td>
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</table>

*aNumbers shown in the table may not exactly multiply or sum to totals shown because of rounding.

*bMarket share analysis performed by IntrinsiQ LLC (Waltham, MA) using proprietary nonpublished data for 2007.

*cMarket share analysis performed by study authors using proprietary nonpublished data from IntrinsiQ LLC (Waltham, MA) for 2008.

*dMarket share analysis performed by study authors using proprietary nonpublished data from IntrinsiQ LLC (Waltham, MA) for January 2008 to January 2009 as a basis for forecasting.

*eTamoxifen, anastrozole, goserelin.

ATC-p=pretreated with anthracyclines, taxanes, and capcitabine; IXA=ixabepilone; MBC=metastatic breast cancer.

Both AT-p and ATC-p patients. The reason for the low PMPM is primarily attributable to the size of the population estimated to receive ixabepilone therapy.

In another analysis of the budget impact of adding erlotinib to a regimen of gemcitabine as first-line treatment of locally advanced, nonresectable, or metastatic pancreatic cancer in the United States, for a hypothetical managed care plan of 500,000 members, with 43 patients newly diagnosed with pancreatic cancer each year, of whom 10 would be treated with gemcitabine+erlotinib, it was found that the new regimen would have a budget impact of $0.02 PMPM.37 Similar to the present study, the authors attributed the relatively low budgetary impact to the small patient population eligible to receive treatment.

Budget impact analyses have become an essential part of a comprehensive economic assessment of health care technology and are increasingly required, along with cost-effectiveness analyses, in decision making.16 Budget impact models are a valuable tool to health plans for making formulary or reimbursement decisions. Such models allow managed care organizations to gauge the potential economic impact resulting from the introduction of a new pharmacological treatment on medical and pharmacy budgets.38 In this model, using our current assumptions, the results suggest that the incremental cost impact to a pharmacy budget on a PMPM basis of adding ixabepilone is relatively small if the drug is used only in accordance with its current FDA-approved indications.

**Limitations**

As with all modeling exercises, our study has its limitations and has employed a number of assumptions. First, our model considers ixabepilone to be used only according to the FDA-approved label indications for MBC. Additional off-label uses, such as for cancers other than treatment-resistant MBC, were not considered in the model analysis.

Second, the model does not consider any nonformulary costs. As ixabepilone is a branded drug, it is more costly than generic drugs.
### TABLE 4
Total Annual Pharmacy Costs in Pre- and Post-Ixabepilone Market Scenarios, Incremental Budget Impact, and PMPM Costs for AT-P Population for Years 1 Through 3

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Pre-IXA</th>
<th>Post-IXA Year 1</th>
<th>Post-IXA Year 2</th>
<th>Post-IXA Year 3</th>
<th>Incremental Budget Impact</th>
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</thead>
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<tr>
<td></td>
<td># Pts</td>
<td>Total Annual Cost ($)</td>
<td># Pts</td>
<td>Total Annual Cost ($)</td>
<td># Pts</td>
</tr>
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<td>Bevacizumab</td>
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<td>9.69</td>
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<td>104</td>
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<td>55,511</td>
</tr>
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<td>Paclitaxel, albumin bound</td>
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</tr>
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<td>1,489,821</td>
<td>96.85</td>
<td>1,512,925</td>
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</table>

\*Numbers shown in the table may not exactly multiply or sum to totals shown because of rounding.
\*Calculated using WAC list price (FirstDataBank Inc., San Bruno, CA),\*23 accessed on March 2009, manufacturers’ product information sheets for dosing,21-23 and assumptions about the median cycle lengths for all drug therapies that were based on the opinions of physicians employed or retained by the study sponsor.

\*Other = tamoxifen, anastrozole, goserelin.

AT-P = pretreated with anthracyclines and taxanes; IXA = ixabepilone; PMPM = per member per month; Pts = patients; WAC = wholesale acquisition cost.

MBC treatment options and thus would be associated with higher administration charges compared with less expensive treatment options. However, the MBC patient population estimated to be eligible to receive ixabepilone therapy is relatively small, thus making any additional costs imposed upon the overall budget to be minor. This assumption was tested in our sensitivity analysis by varying the price of ixabepilone +/- 50%, which did not appear to have a significant impact on the results.

A third potential limitation may be inherent in the market data that were used for the analysis. The AT-P and ATC-P prevalence rates were taken from 2007 market research data for 36 states that were purchased from a proprietary source. The real-world drug utilization data from January 2007 to January 2009 used as the basis for the pre- and post-ixabepilone market share data were also purchased from the same proprietary source. Although we believe that these market data are the best available, there is the potential for over- or underestimation of prevalence rates or market shares for any given drug attributable to the way the data are collected and aggregated. However, it is expected that these limitations should apply to all of the market shares values attained. We tested this uncertainty by varying the projected ixabepilone market uptake in a +/- 50% range, which did not appear to have a significant impact on the results.

**Conclusion**

Given the estimated number of patients eligible for ixabepilone monotherapy in a hypothetical 1 million-member population (15 MBC patients, comprised of both AT-P and ATC-P patients), this budget impact model predicted a relatively minimal incremental budget impact following the introduction of coverage for ixabepilone in accordance with its labeled indications. The estimated incremental increase shared across all plan members in 2009 dollars was at most $0.006 PMPM for each year during the analyzed 3-year period.
**TABLE 5**  
Total Annual Pharmacy Costs in Pre- and Post-Ixabepilone Market Scenarios, Incremental Budget Impact, and PMPM Costs for ATC-p Population for Years 1 Through 3

<table>
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<th>C1xC8</th>
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<th>C12/(1x10^9)/12</th>
<th>C9-C3</th>
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### Annual Pharmacy Cost ($)^b
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<th>Post-IXA Year 2</th>
<th>Post-IXA Year 3</th>
<th>Year 1 Total</th>
<th>Year 1 PMPM</th>
<th>Year 2 Total</th>
<th>Year 2 PMPM</th>
<th>Year 3 Total</th>
<th>Year 3 PMPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>13,484.80</td>
<td>29.63</td>
<td>394,849</td>
<td>27.64</td>
<td>372,723</td>
<td>28.44</td>
<td>383,509</td>
<td>28.34</td>
<td>382,111</td>
<td>-26,766</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>8,356.86</td>
<td>7.41</td>
<td>61,893</td>
<td>7.02</td>
<td>58,706</td>
<td>6.83</td>
<td>57,097</td>
<td>6.84</td>
<td>57,127</td>
<td>-3,188</td>
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<td>Cyclophosphamide</td>
<td>5,092.00</td>
<td>4.44</td>
<td>22,628</td>
<td>4.21</td>
<td>21,462</td>
<td>4.10</td>
<td>20,874</td>
<td>4.10</td>
<td>20,885</td>
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<td>Doxorubicin</td>
<td>396.00</td>
<td>2.96</td>
<td>1,173</td>
<td>2.81</td>
<td>1,113</td>
<td>2.73</td>
<td>1,082</td>
<td>2.73</td>
<td>1,083</td>
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<td>Paclitaxel (liposomal)</td>
<td>396.00</td>
<td>5.93</td>
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<td>2,225</td>
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<td>5.47</td>
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<td>364,693</td>
<td>17.58</td>
<td>309,077</td>
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<td>310,901</td>
<td>17.73</td>
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<td>Pachetaxel</td>
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<td>10.37</td>
<td>60,090</td>
<td>9.83</td>
<td>56,906</td>
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<td>55,433</td>
<td>9.57</td>
<td>55,463</td>
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<tr>
<td>Pachetaxel, albumin bound</td>
<td>23,956.31</td>
<td>17.78</td>
<td>423,825</td>
<td>16.86</td>
<td>403,895</td>
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<td>392,824</td>
<td>16.41</td>
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<td>Trastuzumab</td>
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<td>134,402</td>
<td>4.21</td>
<td>132,223</td>
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<td>4.10</td>
<td>128,668</td>
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<tr>
<td>Vinorelbine</td>
<td>22,512.00</td>
<td>19.26</td>
<td>433,499</td>
<td>16.32</td>
<td>367,390</td>
<td>16.42</td>
<td>369,558</td>
<td>16.46</td>
<td>370,641</td>
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<tr>
<td>Otherc</td>
<td>22,512.00</td>
<td>9.00</td>
<td>200,076</td>
<td>8.00</td>
<td>183,070</td>
<td>9.00</td>
<td>193,074</td>
<td>9.00</td>
<td>193,074</td>
<td>-17,006</td>
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<td>Ixabepilone</td>
<td>20,898.00</td>
<td>0.00</td>
<td>259,650</td>
<td>12.00</td>
<td>259,650</td>
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<td><strong>Totals</strong></td>
<td>219,409.00</td>
<td>148.00</td>
<td>2,241,566</td>
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<td>2,462,994</td>
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<td>2,468,802</td>
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<th>Year</th>
<th>Annual Pharmacy Cost ($)</th>
<th># Pts</th>
<th>Total Annual Cost ($)</th>
<th>Annual Pharmacy Cost ($)</th>
<th># Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>193,074</td>
<td>8</td>
<td>233,074</td>
<td>9</td>
<td>259,650</td>
</tr>
<tr>
<td>2</td>
<td>193,074</td>
<td>9</td>
<td>233,074</td>
<td>9</td>
<td>259,650</td>
</tr>
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<td>3</td>
<td>193,074</td>
<td>9</td>
<td>233,074</td>
<td>9</td>
<td>259,650</td>
</tr>
</tbody>
</table>

### Incremental Budget Impact

<table>
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<tr>
<th>Year</th>
<th>Incremental Budget Impact</th>
<th># Pts</th>
<th>Total Incremental Budget Impact</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>-17,006</td>
<td>9</td>
<td>-17,006</td>
</tr>
<tr>
<td>2</td>
<td>-17,006</td>
<td>9</td>
<td>-17,006</td>
</tr>
<tr>
<td>3</td>
<td>-17,006</td>
<td>9</td>
<td>-17,006</td>
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### PMPM Costs

<table>
<thead>
<tr>
<th>Year</th>
<th>PMPM Costs for ATC-p Population</th>
<th># Pts</th>
<th>Total PMPM Costs for ATC-p Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-17,006</td>
<td>9</td>
<td>-17,006</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>-17,006</td>
<td>9</td>
<td>-17,006</td>
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</tbody>
</table>

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**DISCLOSURES**

This study was funded by Bristol-Myers Squibb Company (BMS), and 3 of the authors (Zhang, Corey-Lisle, and Yuan) are employed by BMS Company. Dymaxium Inc. acted as a paid consultant for BMS. Dymaxium built the budget impact model, forecasted market shares for years 2 and 3, and performed the model analyses. Tasks were completed with guidance by BMS. Market data were purchased by BMS from IntrinsiQ and provided to Dymaxium. An abstract based on this study was presented at the International Society of Pharmacoeconomics and Outcomes Research 13th annual meeting in Toronto, Ontario, Canada, May 2008. Yuan was responsible for study concept and design with the assistance of all other authors. Zhang, Ho, and Whillans performed the data collection. Ho performed data interpretation and wrote the manuscript, with the assistance of the other authors. Revisions were made primarily by Ho.

**REFERENCES**

Budget Impact Analysis of Ixabepilone Used According to FDA-Approved Labeling in Treatment-Resistant Metastatic Breast Cancer


ABSTRACT

BACKGROUND: Community pharmacies vary widely in terms of ownership structures, location, and dispensing policies. It is unknown if an association exists between the type of community pharmacy and the degree of medication adherence exhibited by patrons-patients.

OBJECTIVE: To describe adherence to statin therapy among subjects patronizing different types of community pharmacy categories (department-mass merchandise, chain-franchise, and independent-banner) in Saskatchewan, Canada, between 2000 and 2005.

METHODS: Study data were obtained from the Saskatchewan Drug Plan and Extended Benefits database, which is maintained by the government of Saskatchewan, Canada. The study included all subjects who (a) filled a statin prescription within selected community pharmacies between January 1, 2000, and December 31, 2005; (b) had no record of statin prescriptions during the year prior to the first statin prescription, according to the records of the Saskatchewan Drug Plan and Extended Benefits; and (c) demonstrated active utilization in the drug plan database for at least 1 year after the first statin prescription. The proxy criterion for activity was any dispensing record for statin or nonstatin medications at least 1 year following the index claim. Statin adherence level was estimated as tablets per day, defined as the total number of tablets dispensed divided by the total number of days of observation. Each subject’s observation period began on the index date and ended on the earlier of (a) 30 days after the last record-fill for any type of prescription medication (statin or nonstatin), or (b) December 31, 2005. The primary end point was the proportion of subjects within each pharmacy category who maintained an adherence level of 80% or greater during their individual observation period. Additional adherence calculations were performed for each of 3 time periods, beginning on the index date and ending on days 365, 729, and 1,094 (i.e., 1, 2, and 3 years). Patients were included in the analysis for each time period if they met a proxy criterion for availability for observation, defined as the dispensing of any drug at least 1 day after the end date of each period. Pearson chi-square tests were used to assess the significance of differences in baseline characteristics and adherence proportions, comparing pharmacy categories. Logistic regression analysis estimated the odds of an adherence level of at least 80% during the individual observation period, adjusting for pharmacy category, sex, age 65 years or older, known low-income drug coverage, number of distinct drug classes filled concurrently during the first year of observation, loyalty to index pharmacy, and length of observation. Using similar methods, we also estimated “pharmacy loyalty” by calculating the proportion of subjects who refilled 75% or more of their statin prescriptions at the pharmacy that dispensed their first statin prescription.

RESULTS: From an initial sample of 12,818 subjects who had at least 1 pharmacy claim for a statin in the period from January 1, 2000, through December 31, 2005, 8,699 subjects met the inclusion criteria. Subjects were observed for a mean (SD, range) of 3.7 (1.7, 1.0-7.0) years after the index statin prescription. During the first year following the index claim, statin adherence rates were at least 80% for 1,799 of 3,761 (47.8%) patrons of department-mass merchandise, 1,778 of 3,255 (55.0%) patrons of chain-franchise, and 921 of 1,703 (54.1%) patrons of independent-banner stores (P<0.001). Measured from the index date through day 1,094, 869 of 2,292 (37.9%), 874 of 1,887 (46.3%), and 457 of 975 (46.9%) subjects in the department-mass merchandise, chain-franchise, and independent-banner categories, respectively, had a statin adherence level of at least 80% (P<0.001). In logistic regression analysis, pharmacy category type was significantly associated with statin adherence; subjects in the chain-franchise and independent-banner categories were more likely to be adherent to their statin medications during their observation periods than were those in the department-mass merchandise category (adjusted odds ratio [OR] = 1.36, 95% CI = 1.23-1.50, P<0.001 and OR = 1.39, 95% CI = 1.24-1.57, P<0.001, respectively). From the index date through day 1,094, 1,752 of 2,292 (76.4%), 1,475 of 1,887 (78.2%), and 795 of 975 (81.5%) subjects remained pharmacy-loyal in the department-mass merchandise, chain-franchise, and independent-banner categories, respectively (P=0.006).

CONCLUSION: One year after their first statin fill, subjects demonstrated low rates of adherence, ranging from 48% to 55%, regardless of the type of pharmacy they patronized. Although the differences by type of pharmacy reached statistical significance, their clinical importance is not evident, reinforcing the fact that the problem of nonadherence appears to exist among all types of community pharmacies, regardless of their categorization.
In Canada, most prescription medications are dispensed by licensed pharmacists through community pharmacies. Because of their frequent contact with patients, it has been suggested that community pharmacists are in an ideal position to identify and improve medication nonadherence. However, community pharmacies can vary widely in terms of ownership structures, location, and dispensing policies. It is possible that these organizational policies could influence medication-taking behavior among certain patients.

Little is known about the impact that different types of community pharmacies have on medication adherence. It has been suggested that independently owned pharmacies provide better service, but these observations have not been confirmed by objective data. A recent study by Kalsekar et al. found slightly higher adherence in subjects receiving oral hypoglycemic agents at independent pharmacies compared with chain pharmacies. However, the adherence measure was not applied to subjects that discontinued their therapy, and only 2 types of pharmacies were compared. A second study by White et al. determined that subjects using a mail service pharmacy exhibited a higher degree of adherence to statins than those who used community pharmacies. However, the comparison was limited to a single mail order pharmacy where financial incentives were provided to clients for using this service. Also, no distinction was made between the types of community pharmacies used for comparison.

Medication nonadherence is a global problem and is a predictor of negative patient outcomes. Although many studies have examined predictors of medication adherence, few have examined whether distinct categories of community pharmacies influence medication adherence. Because limited information is available, we designed a preliminary and exploratory study to evaluate whether general trends in medication adherence can be identified among subjects patronizing different categories of community pharmacies between 2000 and 2005.

### Methods

#### Data Source

All study data were obtained from the Saskatchewan Drug Plan and Extended Benefits database, which is maintained by the government of Saskatchewan, Canada. All Saskatchewan pharmacies are equipped with electronic point-of-service terminals that submit to the drug plan fields such as patient identifier, date of dispensing, product name, and quantity. A days supply variable was not captured during the period of study. The drug plan database also contains drug coverage information for known low-income (e.g., social assistance) subjects. Prescription fills for medications listed in the comprehensive provincial formulary are captured for approximately 90% of the province’s population of nearly 1 million. Residents ineligible for coverage under the drug plan include approximately 9% of the population (primarily Registered Indians) whose prescription costs are paid by another government agency.

#### Subject Selection

We created a retrospective cohort study using a new-user design of all drug plan beneficiaries filling a new statin prescription in selected community pharmacies between January 1, 2000, and December 31, 2005. A new statin prescription was defined as having no fills for a statin drug in the previous year as recorded by the Saskatchewan Drug Plan and Extended Benefits. In the year prior to the index statin prescription, 88.4% of subjects (7,693 of 8,699) filled at least 1 prescription for a medication other than a statin. The mean (SD) duration between the first recorded prescription in the previous year and the date of the index statin prescription was 269 (128) days. Because we used prescription fills as a proxy for beneficiary status, we cannot be entirely sure that all patients were truly new users. However, the proportions of subjects without prior fills were distributed evenly among the pharmacy categories used in the present study (ranging from 10.9% to 12.0%, \( P = 0.487 \)). Sensitivity analyses excluding these patients from the analysis produced similar results (data available on request). The statin class of medications was selected for analysis because adherence to these medications is known to be poor, and our research group has experience with statin adherence analyses using Saskatchewan health data.

#### Community Pharmacy Selection

Community pharmacy companies that provide service to the urban centers in Saskatchewan were subjectively grouped into...
3 categories on the basis of typical store type: department-mass merchandise, chain-franchise, and independent-banner\textsuperscript{13} (Table 1). Department-mass stores are large chains that sell a wide variety of merchandise. Typically, a pharmacy department is included in these stores as just 1 of many departments that may also include clothing, sporting goods, groceries, and housewares. In Saskatchewan, department-mass merchandise stores are often referred to as “big-box” stores because of their physical appearance. Chain-franchise stores are also large chains but are devoted primarily to the practice of pharmacy. Although additional types of merchandise, especially health products, vitamins, and cosmetics, are sold in these stores, the primary and central activity is the dispensing of prescriptions. Finally, Saskatchewan still has a number of active pharmacies that are owned and operated by a single individual (owner-operator). They are generally small and located in residential communities, functioning like the “corner store.” For buying purposes, these independent pharmacies sometimes cooperate under a single “banner” in order to obtain better discounts on their wholesale products. However, even if they share the same banner, they continue to operate independently.

A list of pharmacies servicing Saskatchewan was categorized as above and provided to Saskatchewan Drug Plan and Extended Benefits personnel who independently selected a representative sample of community pharmacies to be included in our study. In order to ensure that researchers were blinded, drug plan personnel excluded stores that newly opened or closed during the observation period because it might have been possible for the investigators to identify specific pharmacies by comparing relevant dates from the data provided.

Ultimately, 6 department-mass merchandise stores representing 2 companies (chains), 12 separate chain-franchise stores representing 3 companies (chains), and 16 independent-banner stores were selected. Although this sampling procedure was not random, it was performed by government employees who were not involved in the study. All except 1 of the selected pharmacies were located in the 2 largest centers in Saskatchewan and represented approximately 35% of all pharmacies in these 2 cities (n = 93). These pharmacies provided over 3,000 new statin users from each of the department-mass category and the chain-franchise category. However, because the number of subjects receiving statin prescriptions from the independent-banner category was much lower, selection of 16 stores resulted in approximately 1,700 eligible subjects to represent this cohort. Subject- and store-specific information was de-identified by Saskatchewan Drug Plan personnel before being provided to the researchers. All statin fills in the selected pharmacies were distinguished by a unique pharmacy identifier. Statin and other prescriptions filled in other (nonstudy) Saskatchewan pharmacies were captured, but the pharmacy type could not be distinguished.

### Outcome Measures and Observation Period

Subjects were divided into 3 cohorts based on the type of pharmacy that dispensed the first (i.e., index) statin prescription: department-mass merchandise, chain-franchise, and independent-banner. Individual subject observation periods began on the date of the index prescription and were censored 30 days after the last recorded fill for any type of prescription medication or at the end of the observation period (i.e., December 31, 2005). Only those subjects with an observation period of at least 1 year were included.

The primary end point was the proportion of patients within each category remaining adherent to statin medications. Subjects were classified as adherent if they exhibited at least 80% adherence (optimal adherence) over their observation period. The 80% threshold is easily defined and commonly used in similar studies measuring adherence.\textsuperscript{6,11,14} Subjects with an adherence of greater than 100% were included in the analysis. However, only 1% of the subjects exhibited an adherence of greater than 110%, and the distribution was similar among pharmacy categories (data available upon request). Since subjects could switch pharmacies during the observation period, we calculated the proportion of subjects in each category who remained loyal to their original pharmacy as a secondary end point. Subjects were classified as pharmacy-loyal if 75% or more of their total statin prescriptions were dispensed from the pharmacy where the index prescription was filled.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Categorization of Canadian Community Pharmacies</th>
<th>Department-Mass Merchandise</th>
<th>Chain Franchise</th>
<th>Banner</th>
<th>Independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of dispensary (square feet)</td>
<td>683</td>
<td>786</td>
<td>1,012</td>
<td>877</td>
</tr>
<tr>
<td>Size of frontshop (square feet)</td>
<td>7,496</td>
<td>3,771</td>
<td>6,279</td>
<td>2,484</td>
</tr>
<tr>
<td>Dispensary hours open (weekly)</td>
<td>69</td>
<td>69</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>Average annual prescription volume</td>
<td>33,752</td>
<td>71,617</td>
<td>84,292</td>
<td>62,008</td>
</tr>
<tr>
<td>Annual sales ($ millions)</td>
<td>2.58</td>
<td>4.42</td>
<td>5.91</td>
<td>2.62</td>
</tr>
</tbody>
</table>

Adapted from: The Pharmacy Group. Trends and Insights 2007.\textsuperscript{13}
Data Analysis

Adherence was estimated using the “tablets per day” calculation. The tablets per day measure is calculated by taking the total number of tablets dispensed divided by the total number of days of observation. For example, 80 tablets dispensed over a 100-day observation period would be calculated as 80% adherence. Switching between statin medications was allowed. This method is considered reliable because statins are almost exclusively administered as a single daily dose. In addition, it has been used previously to assess statin adherence using administrative data, and we have found it to be highly correlated to another measure of adherence, the fill frequency. Persistence was estimated as the length of time between the index prescription and date of discontinuation. The date of discontinuation was defined as the earlier of the last recorded statin fill date during the subject’s individual observation period or the end of the study period (December 31, 2005).

Baseline characteristics of subjects and adherence rates among the 3 pharmacy categories were compared using Pearson chi-square tests. Multivariate logistic regression analyses were used to evaluate the association between pharmacy categories and subject adherence throughout the entire observation period, as well as to evaluate pharmacy loyalty. In the models, optimal adherence (less than 80% vs. at least 80%) was the dichotomous dependent variable of interest. In addition to the pharmacy category attended, a number of patient-level covariates were also included: years of observation, known low-income drug coverage, number of distinct drug categories (by American Hospital Formulary Service [AHFS] classification) filled concurrently during the first year of observation, sex, age 65 years or older, and loyalty to the index pharmacy. All first-order interactions were evaluated with none significant. In addition to calculating overall adherence, measured throughout the entire observation period for each subject, we also calculated adherence during 3 time periods beginning on the index date and ending, respectively, at 1 year (365 days), 2 years (729 days), and 3 years (1,094 days) after the start of statin therapy. In order to qualify for these adherence calculations, subjects were required to have an observation period that ended after the year of interest. In other words, subjects were required to have filled a prescription of any type (statin or nonstatin) in the year subsequent to the one being evaluated.

In a sensitivity analysis, we calculated adherence for statins using a different method, the fill frequency (dispensings per months of observation) and re-analyzed the data as described above. This sensitivity analysis resulted in trends similar to our primary analysis (data not shown).

Analyses were carried out using SPSS version 16.0 for Windows (SPSS, Inc., Chicago, IL). The study protocol was granted a letter of exemption by the University of Saskatchewan Biomedical Research Ethics Board.

Results

Overall, 12,818 subjects filled at least 1 statin prescription at the selected pharmacies between 2000 and 2005. Subjects with statin fills recorded in the prior year (n=3,709) and those with an observation period less than 1 year (n=410) were excluded, leaving 8,699 new users of statin therapy eligible for analysis.
TABLE 3  Number and Percent of Subjects Adherent to a Statin Overall and During 1-Year, 2-Year, and 3-Year Periods*  

<table>
<thead>
<tr>
<th>Pharmacy Category</th>
<th>Number of subjects</th>
<th>Overall Adherence (n=3,235)</th>
<th>Index Through Year 1b</th>
<th>Index Through Year 2b</th>
<th>Index Through Year 3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department-mass merchandise</td>
<td>1,414 / 3,761 (37.6)</td>
<td>8,669 (45.0%)</td>
<td>1,799 / 3,761 (48.7)</td>
<td>1,203 / 3,008 (40.0)</td>
<td>869 / 2,592 (33.9)</td>
</tr>
<tr>
<td>Chain-franchise</td>
<td>1,456 / 3,235 (45.0)</td>
<td>1,778 / 3,235 (55.0)</td>
<td>1,255 / 2,575 (48.7)</td>
<td>874 / 1,887 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Independent-banner</td>
<td>784 / 1,703 (46.0)</td>
<td>921 / 1,703 (54.1)</td>
<td>663 / 1,338 (49.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adherence was defined as tablets per day (number of tablets dispensed divided by the total number of days of observation) equal to at least 80% during each of the 3 observation periods. Overall adherence was measured throughout each subject’s entire observation period. Each subject’s observation period began on the date of the index prescription and was censored on the earlier of 30 days after the last recorded fill for any type of prescription medication or the end of the observation period (i.e., December 31, 2005). Results for the 1-, 2-, and 3-year time periods, respectively, were measured from the index date through 365, 729, and 1,094 days. Because we did not have eligibility data, the results for each time period include only subjects with at least 1 prescription claim for any medication filled after the end of the time period.

Comparisons of proportion of subjects with adherence of at least 80% among all 3 pharmacy categories using Pearson chi-square tests were significant (P < 0.001) for all time periods measured.

Cells indicate number adherent/total number (%).

FIGURE 1  Sample Selection Flowchart

Subjects with ≥ 1 statin fill between January 1, 2000, and December 31, 2005 (n=12,818)

Eligible for analysis (n=8,699)
- Statin use during previous 1 year (n=3,709)
- <1-year observation period (n=410)

Excluded (n=4,119)

Observation periods began on the date of the index prescription and were censored on the earlier of 30 days after the last recorded fill for any type of prescription medication or the end of the observation period (i.e., December 31, 2005).

(Figure 1). Few differences in baseline characteristics were observed among the 3 categories (Table 2). Subjects in the chain-franchise cohort were younger than those in the department-mass or independent-banner categories, whereas subjects in the independent-banner category filled prescriptions for more classes of concurrent medications and had a slightly higher proportion of known low-income drug coverage compared with subjects in the other 2 categories. Mean length of observation for all subjects was 3.7 years (range 1.0-7.0 years), and the majority of subjects in each pharmacy category had an observation length of at least 3 years.

Measured throughout each subject’s entire observation period, 37.6% (1,414 of 3,761) of patrons of department-mass merchandise stores, 45.0% (1,456 of 3,235) of patrons of chain-franchise stores, and 46.0% (784 of 1,703) of patrons of independent-banner stores had a statin adherence rate, measured as tablets per day, of at least 80% (P < 0.001; Table 3). During the same time period, mean tablets per day of observation were 0.632, 0.573, and 0.632 in the department-mass merchandise, chain-franchise stores, and independent-banner categories, respectively (P < 0.001 by 3-way Analysis of Variance; data not shown). Mean persistence (length of time between first and last statin fill) was 2.8 years in both the department-mass merchandise and chain-franchise categories and 2.9 years in the independent-banner category (P = 0.587; data not shown).

During the first year following the index statin prescription, 1,799 of 3,761 (47.8%), 1,778 of 3,235 (55.0%), and 921 of 1,703 (54.1%) subjects in the department-mass merchandise, chain-franchise, and independent-banner categories, respectively, had an adherence level of 80% or more (P < 0.001; Table 3). Adherence among subjects in all 3 pharmacy categories continually declined over the 3 years. Of subjects with an observation period of at least 3 years (n = 5,154), 869 of 2,292 (37.9%) department-mass merchandise, 874 of 1,887 (46.3%) chain-franchise, and 457 of 975 (46.9%) independent-banner subjects remained adherent to statin therapy (P < 0.001).

In logistic regression analysis, pharmacy category type was significantly associated with overall statin adherence (Table 4). Subjects in the chain-franchise and independent-banner categories were more likely to be adherent to their statin medications during their observation periods than were those in the department-mass merchandise category (adjusted odds ratio [OR] = 1.36, 95% CI = 1.23-1.50, P < 0.001, and OR = 1.39, 95% CI = 1.24-1.57, P < 0.001, respectively). No significant difference was observed when comparing the chain-franchise with independent-banner categories (adjusted OR = 0.98, 95% CI = 0.87-1.10, P = 0.717; data not shown). Adherence of at least 80% was more likely for subjects aged 65 years or older than for younger subjects (P < 0.001) and for those receiving 1 or more concurrent prescription medications than for those receiving no concurrent medications (P < 0.01). Female sex and low-income drug coverage were associated with less optimal adherence (P ≤ 0.001).

Loyalty to the index pharmacy was high, and among subjects...
In our study of community pharmacy categories, we found significant differences in adherence to statin therapies. Compared with patrons of department-mass merchandise stores, patrons of chain-franchise and independent-banner stores were more likely to remain adherent to statin medications, as measured by tablets per day of 80% or more, independent of age, sex, concurrent medication use, or known low-income drug coverage. No significant difference in statin adherence was observed between the chain-franchise and independent-banner stores. Mean tablets per day of observation for patrons of department-mass merchandise and independent-banner stores were approximately equal, and mean persistence was approximately 2.8 to 2.9 years regardless of pharmacy type.

Kalsekar et al. found that subjects receiving oral hypoglycemic

Discussion

with 3 years of observation (n=5,154), 1,752 of 2,292 (76.4%) in the department-mass merchandise, 1,475 of 1,887 (78.2%) in the chain-franchise, and 795 of 975 (81.5%) in the independent-banner pharmacy categories filled more than 75% of their statin prescriptions at their index pharmacy (P=0.006; Table 5). Overall, subjects in the independent-banner pharmacy category were more likely to remain loyal to their index pharmacy than were those patronizing department-mass merchandise (adjusted OR=1.34, 95% CI=1.16-1.54, P<0.001; Table 6) or chain-franchise stores (adjusted OR=1.22, 95% CI=1.06-1.42, P=0.009; data not shown). No significant difference in subject pharmacy loyalty was observed when comparing the chain-franchise with department-mass merchandise categories (adjusted OR=1.10, 95% CI=0.99-1.23, P=0.084).

Table 4: Predictors of Statin Adherence During Entire Observation Perioda

<table>
<thead>
<tr>
<th>Predictor</th>
<th>n</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Department-mass merchandise</td>
<td>3,761</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chain-franchise</td>
<td>3,235</td>
<td>1.36 (1.24-1.50)</td>
<td>1.36 (1.23-1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Independent-banner</td>
<td>1,703</td>
<td>1.42 (1.26-1.59)</td>
<td>1.39 (1.24-1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4,805</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,894</td>
<td>0.84 (0.77-0.91)</td>
<td>0.79 (0.72-0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 65 years</td>
<td>5,496</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>65 years or older</td>
<td>3,203</td>
<td>1.33 (1.21-1.45)</td>
<td>1.24 (1.13-1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Known low-income drug coveragec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7,356</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,343</td>
<td>0.97 (0.86-1.09)</td>
<td>0.81 (0.71-0.92)</td>
<td>0.001</td>
</tr>
<tr>
<td>Observation period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>365-729 days</td>
<td>1,778</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>730-1,094 days</td>
<td>1,767</td>
<td>0.97 (0.86-1.12)</td>
<td>0.98 (0.86-1.12)</td>
<td>0.765</td>
</tr>
<tr>
<td>1,095 days or more</td>
<td>5,154</td>
<td>0.76 (0.68-0.85)</td>
<td>0.78 (0.70-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin loyaltyd</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75%</td>
<td>2,057</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>≥75%</td>
<td>6,642</td>
<td>0.95 (0.86-1.04)</td>
<td>0.89 (0.81-0.99)</td>
<td>0.031</td>
</tr>
<tr>
<td>Concurrent medication classese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>535</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>2,024</td>
<td>1.29 (1.04-1.59)</td>
<td>1.32 (1.07-1.63)</td>
<td>0.011</td>
</tr>
<tr>
<td>3-4</td>
<td>2,515</td>
<td>1.89 (1.54-2.32)</td>
<td>1.92 (1.56-2.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 or more</td>
<td>3,625</td>
<td>2.48 (2.03-3.03)</td>
<td>2.48 (2.02-3.05)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*aAdherence was defined as tablets per day (number of tablets dispensed divided by the total number of days of observation) equal to at least 80%. Each subject's observation period began on the date of the index prescription and was censored on the earlier of 30 days after the last recorded fill for any type of prescription medication or the end of the observation period (i.e., December 31, 2005). Because we did not have eligibility data, the results for each time period include only subjects with at least 1 prescription claim for any medication filled after the end of the time period.

bC-statistic = 0.599.

cIndicates that the patient was receiving some form of prescription benefit (e.g., shared copayments) from the Saskatchewan Drug Plan and Extended Benefits branch of the Saskatchewan government.

dProportion of all statin prescriptions dispensed from the pharmacy where the index prescription was filled.

eConcurrent medication classes during the first year of observation. Based on American Hospital Formulary System (AHFS) classification. CI = confidence interval; OR = odds ratio.
agents at an independent pharmacy had a 1.7% higher adherence compared with those receiving their prescriptions at a chain pharmacy. However, the follow-up period was relatively short (1 year), and their analysis did not include department-mass merchandise pharmacies.

The statin adherence rates observed in the present study after

### TABLE 5

<table>
<thead>
<tr>
<th>Pharmacy Category</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>8,699</td>
<td>6,921</td>
<td>5,154</td>
</tr>
<tr>
<td>Department-mass merchandise (%)</td>
<td>3,225 / 3,761 (85.7)</td>
<td>2,438 / 3,008 (81.1)</td>
<td>1,752 / 2,292 (76.4)</td>
</tr>
<tr>
<td>Chain-franchise (%)</td>
<td>2,777 / 3,235 (85.8)</td>
<td>2,104 / 2,575 (81.7)</td>
<td>1,475 / 1,887 (78.2)</td>
</tr>
<tr>
<td>Independent-banner (%)</td>
<td>1,511 / 1,703 (88.7)</td>
<td>1,136 / 1,338 (84.9)</td>
<td>795 / 975 (81.5)</td>
</tr>
<tr>
<td>P value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.008</td>
<td>0.006</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pharmacy loyalty was defined as at least 75% of all statin prescriptions being dispensed from the pharmacy where the index prescription was filled. Results for the 1-, 2-, and 3-year time periods, respectively, were measured from the index date through 365, 729, and 1,094 days. Because we did not have eligibility data, the results for each time period include only subjects with at least 1 prescription claim for any medication filled after the end of the time period.

<sup>b</sup>P value for 3-way comparison of pharmacy-loyal proportions.

### TABLE 6

<table>
<thead>
<tr>
<th>Predictor</th>
<th>n</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Department-mass merchandise</td>
<td>3,761</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chain-franchise</td>
<td>3,235</td>
<td>1.09 (0.97-1.20)</td>
<td>1.10 (0.99-1.23)</td>
<td>0.084</td>
</tr>
<tr>
<td>Independent-banner</td>
<td>1,703</td>
<td>1.33 (1.15-1.52)</td>
<td>1.34 (1.16-1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>4,805</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>3,894</td>
<td>1.20 (1.08-1.32)</td>
<td>1.22 (1.10-1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>Younger than 65 years</td>
<td>5,496</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>65 years or older</td>
<td>5,203</td>
<td>1.16 (1.04-1.28)</td>
<td>1.19 (1.06-1.33)</td>
<td>0.002</td>
</tr>
<tr>
<td>Known low-income drug coverage</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7,356</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>1,343</td>
<td>0.83 (0.72-0.94)</td>
<td>0.74 (0.64-0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Observation period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>365-729 days</td>
<td>1,778</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>730-1,094 days</td>
<td>1,767</td>
<td>0.89 (0.75-1.06)</td>
<td>0.89 (0.75-1.05)</td>
<td>0.173</td>
</tr>
<tr>
<td>1,095 days or more</td>
<td>5,154</td>
<td>0.56 (0.48-0.64)</td>
<td>0.55 (0.48-0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin adherence&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>5,045</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>≥80%</td>
<td>3,654</td>
<td>0.95 (0.86-1.05)</td>
<td>0.89 (0.81-0.99)</td>
<td>0.029</td>
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<tr>
<td>Concurrent medication classes&lt;sup&gt;4&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<tr>
<td>None</td>
<td>535</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1-2</td>
<td>2,024</td>
<td>1.32 (1.07-1.63)</td>
<td>1.32 (1.06-1.63)</td>
<td>0.012</td>
</tr>
<tr>
<td>3-4</td>
<td>2,515</td>
<td>1.45 (1.17-1.78)</td>
<td>1.42 (1.15-1.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>5 or more</td>
<td>3,625</td>
<td>1.37 (1.08-1.61)</td>
<td>1.26 (1.02-1.56)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pharmacy loyalty was defined as at least 75% of all statin prescriptions being dispensed from the pharmacy where the index prescription was filled.

<sup>b</sup>P value for 3-way comparison of pharmacy-loyal proportions.

<sup>3</sup>Indicates that the patient was receiving some form of prescription benefit (e.g., shared copayments) from the Saskatchewan Drug Plan and Extended Benefits branch of the Saskatchewan government.

<sup>4</sup>Adherence was defined as tablets per day (number of tablets dispensed divided by the total number of days of observation). Because we did not have eligibility data, the results for each time period include only subjects with at least 1 prescription claim for any medication filled after the end of the time period.

<sup>CI</sup> = confidence interval; OR = odds ratio.
3 years (37.9%, 46.3%, and 46.9% for department-mass merchandise, chain-franchise, and independent-banner, respectively) are comparable to those found in previously published studies. Other recent reports have observed statin adherence rates even lower than those reported in the present study. Although nonadherence to statins has been widely cited, it is likely that adherence to other chronic cardiovascular medications is equally poor.

Despite overall low adherence, pharmacy loyalty among our study subjects was high in all 3 pharmacy categories. Independent-banner pharmacies were associated with a greater loyalty over 3 years of observation than were chain-franchise or department-mass merchandise stores (81.5%, 78.2%, and 76.4%, respectively), but the observed differences were small and are of questionable importance. This observation is important because it suggests that individuals commonly rely on a single pharmacy for their chronic medications.

A strength of our study is the real-world evaluation of statin adherence in a sizeable proportion of pharmacy stores that provide service to 2 major cities in Saskatchewan, Canada. Within each store selected, we captured all subjects who were new users of statin therapy. Also, our data appeared reliable in that rates reported from our sample were very similar to those previously reported.

Limitations
Several limitations must be considered. The most important limitation relates to the way we categorized the community pharmacy stores. We categorized the community pharmacy stores in broad categories that may not have captured the important physical or other characteristics that might be associated with differences in customer service and patient education. Larger differences in adherence might have been detected if community pharmacies were categorized by other criteria. Pedan et al. (2007) found that significant variability in statin adherence can be observed within stores belonging to the same national chains.

Second, administrative databases inherently lack detailed patient-level information. Therefore, it is possible that cohorts differed in important clinical, demographic, or socio-economic factors that could not be identified. Although most of the available baseline characteristics except age appeared similar between the categories, we cannot evaluate the extent to which selection bias influenced our results. In other words, we cannot rule out the possibility that adherent patients are more likely to patronize a certain type of pharmacy.

Third, as with all administrative database studies, we assumed that filling a prescription means the medication was actually taken. Although this assumption would appear to be realistic, we cannot say with complete certainty that the medication was consumed. To rule out the possibility that compliance packaging—a practice commonly used in Canada, in which prescriptions are automatically packaged and renewed weekly—might have influenced our results, we analyzed the frequency of prescriptions in each cohort that contained fewer than 14 dispensed tablets. We found this percentage to be very low; therefore, compliance packaging is unlikely to have influenced our results.

Fourth, we calculated adherence using a tablets per day measure instead of a standard calculation because days supply was not captured by Saskatchewan Health and Extended Benefits Branch during the period of this study. However, statins are almost exclusively prescribed once per day. Fifth, we did not have eligibility data and therefore had to depend on a crude measure—the presence of at least 1 prescription drug claim for any medication—to estimate each individual’s ongoing beneficiary status in the database. This proxy could have resulted in removing from the sample patients who were still eligible for benefits. Among patients using a statin as their only medication, the criterion would have resulted in removing nonpersistent statin users from the sample. However, this proxy measure was applied to subjects in all 3 pharmacy categories analyzed so we would not expect it to have influenced the between-group comparisons. Although adherence results at the end of years 2 and 3 might have been affected by the number of patients lost to follow-up, we still had access to over 5,000 subjects with at least 3 years of data. Furthermore, only 410 (3.2%) of all new statin users were excluded because of an observation period less than 1 year, leaving 8,699 subjects available for the 1-year adherence analysis.

Finally, despite the relatively large sample, our pharmacies were not randomly selected. However, the selection process was carried out by personnel at the Saskatchewan Prescription Drug Plan who were not involved in our study and took great care to ensure the privacy and confidentiality of all information provided. Although 35% of all pharmacies providing service to the 2 major urban centres in Saskatchewan were captured and analyzed, these results may not be generalizable to all pharmacies or communities, especially those in rural settings.

Conclusion
During the first year after initiating statin pharmacotherapy, subjects demonstrated low rates of adherence, measured as tablets per day of at least 80%, regardless of the type of pharmacy they patronized (47.8% in department-mass merchandise stores, 55.0% in chain-franchise stores, and 54.1% in independent-banner stores). Although the differences by type of pharmacy reached statistical significance, their clinical importance is not evident. These data reinforce the fact that the problem of nonadherence appears to exist among all types of community pharmacies, regardless of their categorization. Further studies are needed to determine if other methods of categorization (i.e., by clinical service) may help identify characteristics of community pharmacies that influence medication adherence in a positive way.
DISCLOSURES

This study was funded by a research grant from Saskatchewan Health and Merck-Frosst Schering. Charity Evans receives funding through a Canadian Institute of Health Research Clinical Research Initiative Fellowship, and Dean Eurich receives a salary support award from the Alberta Heritage Foundation for Medical Research (Population Health Investigator).

Evans, Blackburn, Eurich, and Lamb contributed the study concept and design. Mansell, Semchuk, and Jorgenson developed the request for data from Saskatchewan Health, with the assistance of Evans. All authors but Lamb contributed to data interpretation. The manuscript was written primarily by Evans with the assistance of the other authors. Revisions were made primarily by Blackburn and Evans.

Disclaimer: This study is based in part on de-identified data provided by the Saskatchewan Prescription Drug Plan. The interpretation and conclusions contained herein do not necessarily represent those of the government of Saskatchewan or the Saskatchewan Prescription Drug Plan.

REFERENCES


Economic Burden of Postoperative Ileus Associated With Colectomy in the United States

Shrividya Iyer, PhD; William B. Saunders, PhD; and Stephen Stemkowski, PhD

ABSTRACT
BACKGROUND: Postoperative ileus, a transient impairment of gastrointestinal motility, is a common cause of delay in return to normal bowel function after abdominal surgery. Colectomy surgery patients who develop postoperative ileus could have greater health care resource utilization, including prolonged hospitalization, compared with those who do not develop postoperative ileus. Very few studies have assessed the impact of postoperative ileus on resource utilization and costs using retrospective analysis of administrative databases.

OBJECTIVE: To assess health care utilization and costs in colectomy surgery patients who developed postoperative ileus versus those who did not.

METHODS: A retrospective cohort study design was used. Adult patients with a principal procedure code for colectomy (ICD-9-CM procedure codes 45.71–45.79), discharged between January 1, 2004, and December 31, 2004, were identified from the Premier Perspective database of inpatient records from more than 500 hospitals in the United States. The colectomy patients were further classified for the presence of postoperative ileus, identified by the presence, in any diagnosis field on the administrative patient records, of a code for paralytic ileus (ICD-9-CM code 560.1) and/or digestive system complications (ICD-9-CM code 997.4) during the inpatient stay. Code 997.4 was used to account for cases in which postoperative ileus would be reported as a complication of anastomosis, as could be the case in colectomy surgeries. Hospital length of stay (LOS) and hospitalization costs were compared using t-tests. Multivariate analyses were performed with log-transformed LOS and log-transformed cost as the dependent variables. Patient demographics, mortality risk, disease severity, admission source, payment type (retropective/prospective), and hospital characteristics were used as covariates.

RESULTS: A total of 17,876 patients with primary procedure code for colectomy were identified, of whom 3,115 (17.4%) patients were classified for presence of postoperative ileus (including paralytic ileus only [n = 1,216; 6.8%], digestive system complications only [n = 383; 2.1%], or both [n = 1,516; 8.5%]). A majority of the colectomy patients with and without postoperative ileus, respectively, were male (54.1% vs. 50.3%, P < 0.001), Caucasian (70.5% vs. 69.3%, P = 0.170), and aged 51–64 years (51.1% vs. 49.7%, P = 0.143). The mean [SD] hospital LOS was significantly longer in patients with postoperative ileus (13.8 [13.3] days) compared with patients without postoperative ileus (8.9 [9.5] days; P < 0.001). Presence of postoperative ileus was found to be a significant predictor of hospital LOS (95% CI = 13.3%–17.7%) in patients undergoing colectomy surgery.

CONCLUSION: Postoperative ileus in colectomy patients is a significant predictor of hospital resource utilization.


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What is already known about this subject
• Postoperative ileus is a temporary impairment of gastrointestinal motility that commonly occurs after abdominal surgery. Although the literature regarding the incidence of postoperative ileus is limited, the incidence rates appear to vary by the type of surgery, with reported incidence rates ranging from 15%-25% in patients undergoing colectomy.
• The etiology of postoperative ileus is understood to be multifactorial with potential causes including inflammation from surgical manipulation, inhibitory neural reflexes, and the use of opioids.
• Although a few pharmacoeconomic studies have been published on postoperative ileus using hospital chart data, no cost study to our knowledge has used large multihospital databases and focused specifically on colectomy surgeries.

What this study adds
• Mean (SD) hospital length of stay (LOS) for colectomy patients with postoperative ileus was 13.8 (13.3) days total, compared with 8.9 (9.5) days total for colectomy patients without postoperative ileus.
• Mean (SD) per stay hospitalization costs for colectomy patients with and without postoperative ileus were, respectively, $25,089 ($35,386) and $16,907 ($29,320).
• In multivariate regression models adjusted for covariates, presence of postoperative ileus was found to be a significant predictor of hospital LOS (29% increase, 95% CI = 26.0%-31.0%) and costs (15.5% increase, 95% CI = 13.3%-17.7%) in patients undergoing colectomy surgery.

Postoperative ileus is a transient impairment of bowel motility following surgery. It can occur following surgical disruption of the abdominal cavity but may also occur following surgery at other sites.1,2 Postoperative ileus is characterized clinically by abdominal distension, decreased or absent bowel sounds, constipation, and inability to advance oral intake. Gradual recovery of gut function occurs sequentially by gut segment, with the colon recovering last.1,3 In abdominal surgery such as colectomy, this process of postoperative bowel recovery typically lasts 3-5 days.4

The pathogenesis of postoperative ileus is thought to involve multiple mechanisms.2 Neural reflexes that inhibit intestinal motility via several different pathways are thought to play a role in the pathogenesis of postoperative ileus.5-7 Inflammation in
the gut wall characterized by activation of resident macrophages in response to manipulation is also considered to play a role in postoperative ileus, and several inflammatory mediators have been implicated in its evolution.\textsuperscript{8-11} Opioid drugs used for postoperative analgesia may also contribute to postoperative ileus by decreasing intestinal motility via stimulation of μ-opioid receptors in the gut.\textsuperscript{12,13}

Postoperative ileus has a profound impact on outcomes. Increased morbidity associated with postoperative ileus includes nausea and vomiting, increased pain, and prolonged time to oral intake of nutrition necessary for wound healing and immune function.\textsuperscript{1,13} Risk of aspiration and increased time to mobilization may lead to pulmonary complications. These consequences of postoperative ileus are associated with greater resource utilization including prolonged hospitalization.\textsuperscript{14,15}

Because dysmotility of the gut may be a factor in delaying hospital discharge following abdominal surgery, several strategies have been developed to speed the return of gut function.\textsuperscript{16} Accelerated postoperative care including early oral feedings, avoidance of nasogastric intubation, and early ambulation may hasten restoration of gut function, reduce morbidity, and shorten hospital stay.\textsuperscript{2,16-18} Less invasive surgery using laparoscopy is effective in reducing time to return of gut function and duration of hospital stay and has been shown to be safe even in patients undergoing colectomy for colon carcinoma.\textsuperscript{19-22} Additional techniques that can be combined in a multimodal approach to prevent and manage postoperative ileus include opioid-sparing analgesia, use of regional anesthesia techniques, and administration of laxatives.\textsuperscript{2,6,23,24} Currently available prokinetic agents have not been proven effective in the treatment or prevention of postoperative ileus;\textsuperscript{2} however, alvimopan, a new pharmacologic agent that antagonizes the effects of opioid analgesia on the gut, has been shown to be helpful in restoring gastrointestinal function and reducing time to hospital discharge.\textsuperscript{25,26}

Although these efforts have been successful in shortening hospital stay and reducing costs, they have some limitations. Laparoscopic surgery remains inappropriate for some patients and unavailable at some centers.\textsuperscript{20,22} In addition, conversion from laparoscopic-assisted to open colectomy is required in some patients; a meta-analysis of 26 studies reported a conversion rate of 14% (range = 0%-42%).\textsuperscript{23} In addition, even among patients who receive accelerated postoperative care to minimize postoperative ileus following bowel resection, postoperative ileus still occurs in many patients; postoperative ileus-related morbidity was reported in 15% of 727 patients who received accelerated postoperative care following open bowel resection.\textsuperscript{27} Therefore, the clinical and economic consequences of postoperative ileus remain a concern in spite of current preventive and management efforts.

Limited recent data are available that elucidate the economic impact of postoperative ileus in patients undergoing colectomy surgeries. This lack of information, as well as availability of newer techniques for addressing postoperative ileus, suggest that older estimates should be updated.\textsuperscript{15} In this retrospective database analysis, we studied the impact of postoperative ileus on health care utilization and costs in patients who underwent open or laparoscopic colectomy. The main objective of our study was to quantify the incremental impact of postoperative ileus on health care utilization, including hospital length of stay (LOS) and hospitalization costs, in patients undergoing colectomy surgery in the United States. We conducted the economic analysis from a hospital perspective using a large hospital alliance database.

\section*{Methods}

\subsection*{Data Source}

A retrospective cohort study was conducted using data from the Premier Perspective database. This repository of hospital administrative data includes approximately one-sixth of all hospitalizations in the United States and was developed for quality and utilization benchmarking. It contains a total of 2.5 billion patient daily service records, and approximately 45 million records are added each month. Annually, nearly 5 million hospital discharges are processed and recorded in the Perspective database. In addition to the data elements available in most standard hospital discharge files, the Perspective database also contains a date-stamped log of all billed items including procedures, medications, laboratory, and diagnostic and therapeutic services at the individual patient level. The Uniform Billing (UB)-92 discharge form provides data on demographic characteristics, discharge diagnoses, and discharge status (including death, but not its cause). Patient records in the database used for this study were de-identified in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Records relating to a common hospital discharge were linked using a non-personal identifier assigned by the data provider that prevented subject identification and the linking of identifiers to subjects.

The data undergo quality checks, and cost information is reconciled with the hospitals’ financial statements. The data are used by hospitals to compare their clinical and financial performance against the performance of their peers. The Premier Perspective database is used in the Centers for Medicare & Medicaid Services Hospital Quality Incentive Demonstration Project, which links reimbursement of hospitals to the quality of patient care and outcomes of care for selected procedures or conditions.\textsuperscript{28} Dollar amounts used in the present study’s analyses represent either costs as recorded in procedural cost accounting systems in 70%-80% of hospitals or estimated costs based on a ratio of cost to charges in the remaining 20%-30%.

\subsection*{Patient Selection Criteria}

To be eligible for analysis, a patient was required to meet the following criteria:

\begin{itemize}
  \item An inpatient discharge during 2004
  \item Aged 18 years or older
  \item A principal procedure code for open or laparoscopic excision
\end{itemize}
of the large intestine (colectomy) International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 45.71-45.79 (Table 1).

The colectomy patients were further classified on the basis of presence or absence of a diagnosis code for postoperative ileus, recorded in any diagnosis field in the administrative record, during the inpatient stay for the colectomy procedure. Diagnosis codes for postoperative ileus included paralytic ileus (ICD-9-CM code 560.1) and/or digestive system complications not elsewhere classified (ICD-9-CM code 997.4). The digestive system complications code (ICD-9-CM 997.4) was included in addition to the code for paralytic ileus (ICD-9-CM 560.1) because code 997.4 includes within it the “complications of intestinal anastomosis.” An anastomosis is a surgical connection between two structures. It usually means a connection that is created between tubular structures, such as blood vessels or loops of intestine, as is the case for colectomy surgeries, in which parts of the colon are removed and the remaining sections are reconnected surgically. Since the primary cohort population for this study consists of patients who had undergone colectomy surgery, code 997.4 could be used to code postoperative ileus as a complication resulting from anastomosis for these patients. Hence, the code was included in an attempt to get a comprehensive estimate of postoperative ileus in this population, even though a significant overlap between the 2 codes was expected in our study results. LOS for patients who expired in the hospital was calculated as the time between date of admission and date of death.

Adjustment for Severity and Mortality Risk

In order to control for confounding factors such as severity of condition and comorbidities, which could impact hospital LOS, All Patient Refined Diagnosis Related Groups (APR-DRGs) were used as covariates. APR-DRGs are a joint development of 3M Health Information Systems and the National Association of Children’s Hospitals and Related Institutions and are used by the Agency for Healthcare Research and Quality (AHRQ) for risk adjustment. APR-DRGs expand the basic DRG structure by adding 2 sets of subclasses to each base APR-DRG.

Each set consists of 4 subclasses and addresses patient differences relating to severity of illness and risk of mortality. Severity of illness is defined as the extent of physiologic decompensation or organ system loss of function. Risk of mortality is defined as the likelihood of dying. Since severity of illness and risk of mortality are distinct patient attributes, separate subclasses are assigned to a patient for each attribute. The 4 severity of illness subclasses and the 4 risk of mortality subclasses are numbered sequentially from 1 to 4 indicating, respectively, minor, moderate, major, and extreme severity of illness or risk of mortality. The underlying clinical principles of APR-DRGs are that the severity of illness and risk of mortality of a patient are highly dependent on the patient’s underlying clinical problems, and that patients with high severity of illness or risk of mortality are usually characterized by multiple serious diseases or illnesses. In the APR-DRGs, the assessment of the severity of illness or risk of mortality of a patient is specific to the base APR-DRG to which a patient is assigned. In other words, the determinations of the severity of illness and risk of mortality are disease-specific.

Statistical Analysis

Descriptive statistics were calculated for demographic (age, race, and gender) and health care characteristics (admission type, admission source, hospital payer type). Hospital LOS, all-cause 30-day readmission rates, and costs for the postoperative ileus and non-postoperative ileus groups were compared using t-tests and chi-square tests as appropriate. In order to assess the incremental hospital days and costs associated with postoperative ileus after accounting for covariates, multivariate regression analyses were performed with log-transformed LOS and costs as dependent variables and presence of postoperative ileus as a key independent variable. Since the distributions of the hospital LOS and costs are positively skewed, natural logarithmic transformations were performed to normalize the data, which is essential to fulfill the assumptions of multivariate regression analysis.

For the LOS model, regression (mixed linear) modeling using the SAS (SAS Institute Inc., Cary, NC) procedure “PROC MIXED” was used to account for the correlation that can be expected among patients treated in a particular hospital and to explore the effects of both hospital characteristics and patient characteristics on LOS. For the cost model, regression modeling using the SAS procedure “PROC REG” was used. Patient demographics (age, gender, and race), APR-DRG mortality risk, APR-DRG case severity, admission source (physician, health maintenance organization [HMO], transfer, emergency room [ER], and other), payment method (retrospective vs. prospective, which includes managed care capitated and Medicaid managed care capitated arrangements), and hospital characteristics (bed size, teaching vs. nonteaching, and urban vs.
Admission and Discharge Characteristics

A significantly lower proportion of patients who developed postoperative ileus compared with those who did not were in category level 1 (minor) for APR-DRG severity (8.0% vs. 38.4%, respectively, \( P < 0.001 \)) and APR-DRG mortality (47.6% vs. 60.2%, \( P < 0.001 \); Table 3). A majority of the colectomy surgery patients in both cohorts had elective surgery, but the elective proportion of admissions was smaller in the group of patients who subsequently developed postoperative ileus than those who did not (49.9% vs. 57.7%, respectively, \( P < 0.001 \)). The admission type was classified as “emergency” for a significantly greater proportion of patients who subsequently developed postoperative ileus than patients who did not (33.0% vs. 28.7%, \( P < 0.001 \)). A majority of the patients in both the ileus and no ileus groups had physician referral as the admission source (59.5% vs. 64.7%, respectively, \( P < 0.001 \)).

Patients who developed postoperative ileus were less likely than those without postoperative ileus to be discharged home rural) were used as covariates in both models. The natural antilogarithms of the parameter estimates were obtained. Specifically, the percentage increase or decrease predicted in the dependent variable by a 1-unit increase in any independent variable is obtained using the formula \( (e^{estimate} - 1) \times 100 \), where \( e \) is a constant approximately equal to 2.718. All analyses were performed using SAS version 9.1.

Results

A total of 17,876 patients with a primary procedure code for colectomy were identified, of whom 3,115 (17.4%) patients had a secondary diagnosis of postoperative ileus, including paralytic ileus only (\( n = 1,216 \), 6.8%), digestive system complications only (\( n = 383 \), 2.1%), and both paralytic ileus and digestive system complications (\( n = 1,516 \), 8.5%; Figure 1). A majority of the colectomy patients with and without postoperative ileus, respectively, were male (54.1% vs. 50.3%, \( P < 0.001 \)), Caucasian (70.5% vs. 69.3%, \( P = 0.170 \)), and aged 51-64 years (51.1% vs. 49.7%, \( P = 0.143 \); Table 2).

**FIGURE 1** Patient Selection for Colectomy Surgery Patients

Patients included in the Premier Perspective database, selection period January 1, 2004 through December 31, 2004

N = approximately 5,000,000 annual inpatient hospital discharges

Patients with a principal procedure code for colectomy (excision of large intestine — ICD-9-CM = 560.1-560.9) and aged 18 years or older

N = 17,876

Patients with a diagnosis of postoperative ileus (ICD-9-CM diagnosis codes 560.1 or 997.4)

\( n = 3,115 \) (17.4%)

Patients with a diagnosis code of paralytic ileus only (ICD-9-CM code 560.1)

\( n = 1,216 \) (6.8%)

Patients with diagnosis codes for both paralytic ileus and digestive system complications (ICD-9-CM codes 560.1 and 997.4)

\( n = 1,516 \) (8.5%)

Patients with a diagnosis code of digestive system complications only (ICD-9-CM code 997.4)

\( n = 383 \) (2.1%)

Patients without a diagnosis of postoperative ileus (ICD-9-CM diagnosis codes 560.1 or 997.4)

\( n = 14,761 \) (82.6%)

after surgery (67.2% vs. 77.4%, respectively, P<0.001) and more likely to be discharged to another institution (7.7% vs. 4.9%, P<0.001) or to home health care (21.7% vs. 15.0%, P<0.001; Table 3). The all-cause 30-day hospital readmission rate was significantly higher for patients with postoperative ileus than for those without (0.9% vs. 0.3%, respectively, P<0.001).

Hospital and Payer Characteristics
A majority of the colectomy surgeries in the groups with and without postoperative ileus, respectively, were performed in nonteaching hospitals (61.5% vs. 62.0%), urban hospitals (83.1% vs. 85.8%), and hospitals with more than 100 beds (96.2% in both groups; Table 4). A majority of admissions in both groups were reimbursed by a noncapitated managed care payment source (61.2% vs. 62.3%). In both groups, the majority of patients were discharged to home health care (21.7% vs. 15.0%, respectively, P<0.001; Table 3).

Hospital Length of Stay and Costs
Mean [SD] hospital LOS in days was significantly higher in colectomy patients with postoperative ileus than in patients without (13.75 [13.33] vs. 8.85 [9.49], respectively, P<0.001; Table 5). The median LOS in the postoperative ileus group was 10 days compared with 6 days in the non-postoperative ileus group. Results were similar for all APR-DRG severity levels. Mean [SD] hospitalization costs were significantly higher for colectomy patients with postoperative ileus than patients without, overall ($25,089 [$35,386] vs. $16,907 [$29,320], respectively, P<0.001) and for the first (lowest) 3 severity levels. Among patients at APR-DRG severity level 4 (extreme severity), the cost difference was not statistically significant (P=0.068).

In the multivariate regression model of hospital LOS on postoperative ileus and covariates, presence of postoperative ileus was found to be a significant predictor (β=0.254, 95% confidence interval [CI]=0.235-0.274, P<0.001), associated with...
TABLE 4  Hospital and Payer Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Postoperative Ileus</th>
<th>Without Postoperative Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Primary payer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managed care: capitated</td>
<td>73</td>
<td>2.3</td>
</tr>
<tr>
<td>Medicaid managed care: capitated</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Charity</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>Commercial: indemnity</td>
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<td>14.8</td>
</tr>
<tr>
<td>Direct employer contract</td>
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<td>0.8</td>
</tr>
<tr>
<td>Indigent</td>
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<td>0.8</td>
</tr>
<tr>
<td>Managed care: not capitated</td>
<td>1,907</td>
<td>61.2</td>
</tr>
<tr>
<td>Medicaid managed care: not capitated</td>
<td>43</td>
<td>1.4</td>
</tr>
<tr>
<td>Medicaid fee for service</td>
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<td>7.7</td>
</tr>
<tr>
<td>Other</td>
<td>66</td>
<td>2.1</td>
</tr>
<tr>
<td>Other government payers</td>
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<td>2.1</td>
</tr>
<tr>
<td>Self-pay</td>
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<td>5.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Workers compensation</td>
<td>11</td>
<td>0.4</td>
</tr>
</tbody>
</table>

| Hospital region                | 329 | 10.6| 2,580|17.5|
| NorthEast                      |    |    |    |    |
| South                         | 1,206| 38.7|4,873|33.0|
| West                          | 435 | 14.0| 1,838|12.5|
| Midwest                       | 1,145| 36.8|5,470|37.1|

| Hospital total beds            | 117 | 3.8| 560 | 3.8|
| 0-100                          |    |    |    |    |
| 101-500                        | 1,729| 55.5|8,583|58.1|
| >500                           | 1,269| 40.7|5,618|38.1|

| Hospital type                  | 528 | 17.0| 2,091|14.2|
| Rural                          |    |    |    |    |
| Urban                          | 2,587| 83.0|12,670|85.8|

| Teaching status                | 1,915| 61.5| 9,150|62.0|
| Non-teaching                   |    |    |    |    |
| Teaching                       | 1,200| 38.5| 5,611|38.0|

Discussion

Our study results indicate that postoperative ileus occurs in approximately 17% of the colectomy surgeries performed in the hospitals in the Premier Perspective database, which represents approximately one-sixth of hospital discharges in the United States. The rates of postoperative ileus vary from 4%-75% in studies reported in the literature for abdominal surgeries.15,31-33 The rates of postoperative ileus found in this database seem to be similar to those reported in other studies that have used ICD-9-CM codes for identification of cases of postoperative ileus in colectomy patients. In a study by Goldstein et al., the incidence of postoperative ileus in abdominal surgeries was reported to be 8.5%, with the highest incidence in large and small bowel resection (14.9% and 19.2%, respectively).15 In a pooled analysis of clinical studies of a drug aiming to prevent postoperative ileus in patients following bowel resection surgery, the rate of postoperative ileus was approximately 15% in patients treated with placebo.27

While comparing across studies in the literature, it is important to emphasize the variability in the definition of the term “postoperative ileus.” The postoperative ileus rate of 17% in colectomy patients found in our study is lower than those reported in studies that have used narrative information in patient charts or a pre-defined cutoff time to recovery of bowel function in addition to ICD-9-CM codes. In a retrospective cohort review of patient chart records at a major academic center in the United States, the rates of prolonged postoperative ileus in 40 hemicolectomy patients was found to be 24.5%.31 In addition to ICD-9-CM codes, that study used additional criteria to identify postoperative ileus, including documentation of postoperative ileus in the narrative section of the chart, confirmation or identification of postoperative ileus by radiological studies such as obstruction series or abdominal or pelvic computed tomography scans, and prolonged return of gastrointestinal function, including lack of bowel sounds, delayed flatus, and no bowel movement, abdominal distention, nausea, or vomiting. In a study reported in a meeting abstract, Benedict et al. reported that the incidence of postoperative ileus, defined as greater than 5 days of time to recovery of normal bowel function, was 52%-75% in patients after colonic surgery in Germany.33

In the present study, we found that postoperative ileus predicts an increase of 29% in the average hospital LOS. Similar results have been reported for total abdominal surgeries and some types of colectomy surgeries, hemicolectomy in particular.15,27,31 LOS is an important outcome as a marker for resource consumption. In a study evaluating the association of postoperative ileus with hospital LOS in abdominal surgeries using the National Inpatient Sample (NIS) database, hospital LOS in patients with postoperative ileus was 2.35 to 3.00 days longer on average compared with patients without postoperative ileus.32 In clinical studies of bowel resection patients, the average LOS has been reported to be 6.6 days.27 In a study of abdominal surgeries, the average hospital...
LOS was found to be 11.5 days for cases with coded postoperative ileus versus 5.5 days for cases without coded postoperative ileus.\textsuperscript{15} Salvador et al. reported that in hemicolecotomy patients, the average hospital LOS was 16.6 days (median 15.8 days) in patients with prolonged postoperative ileus compared with 8.6 days (median: 6.8 days) in patients without any evidence of postoperative ileus.\textsuperscript{31} The results of our study confirm that postoperative ileus in colectomy patients, including hemicolecotomy, could be a significant predictor of hospital LOS, even after controlling for various confounding factors in multivariate analysis. Our study is one of the first to assess the association between postoperative ileus and hospital LOS in colectomy patients in the United States after controlling for other potential confounding factors, such as patient demographics and condition severity.

In addition to prolonged hospital LOS during the index hospitalization, patients developing postoperative ileus are also at higher risk for hospital readmission. The 0.38% rate of 30-day all-cause hospital readmissions found in our study is much lower than those reported in previous studies of abdominal surgeries. Goldstein et al. reported a 30-day readmission rate for postoperative ileus of 3.6% in abdominal surgery patients with postoperative ileus compared with 0.02% in patients without postoperative ileus.\textsuperscript{15} Past studies have reported that approximately 10% of patients undergoing colorectal surgery were readmitted within 30 days, and one-third were readmitted for small-bowel obstruction or ileus.\textsuperscript{34} Lower readmission rates in our study could be attributed to the restricted sample of colectomy surgery cases in the present study compared with all abdominal surgeries as reported in other previously published studies. Nevertheless, the readmission rates found in our study were higher in patients with postoperative ileus than in those without, which could contribute significantly to increased health care costs.

The total annual national hospital cost attributed to managing coded postoperative ileus in abdominal surgeries has been projected to be $1.46 billion for both the index hospitalization and any readmissions within 30 days.\textsuperscript{15} We found that presence of postoperative ileus is associated with an increase of approximately 15% in hospital costs. Other studies have reported incremental costs associated with postoperative ileus in abdominal surgeries. Sarawate et al. reported that the incremental charges attributable to postoperative ileus were found to range between $4,118 and $8,745 per hospitalization in intra-abdominal surgeries.\textsuperscript{32} Goldstein et al. reported that the average hospital cost for cases with coded postoperative ileus following abdominal surgeries was $18,877 compared with $9,460 for cases without any code for postoperative ileus.\textsuperscript{15} Our study confirms that postoperative ileus could be a significant predictor of hospital LOS and costs in patients undergoing colectomy surgery, controlling for covariates.

Limitations
First, since postoperative ileus was identified by ICD-9-CM codes, postoperative ileus rates could be underestimated. Use of information in patient charts in addition to the ICD-9-CM codes could help to account for the underestimation in future research. Second, billing and coding errors could potentially have occurred. Third, few clinical variables were available for inclusion in the multivariate analyses, thus limiting conclusions about the direct contribution of postoperative ileus on hospital LOS and cost. Multivariate analysis controls only for measured covariates, not for unmeasured confounding factors. Fourth, the proportion of surgeries that were performed laparoscopically is unknown. It is possible that differences in surgical procedures could have an effect on LOS and cost outcomes. Finally, this study failed to
TABLE 6  Relationship of Postoperative Ileus With Hospital Length of Stay and Costs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hospital Length of Stay (Log-Transformed) as Dependent Variable(^a)</th>
<th>Hospital Costs (Log-Transformed) as Dependent Variable(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Antilog Estimate</td>
</tr>
<tr>
<td>Intercepts</td>
<td>1.762</td>
<td>5.83</td>
</tr>
<tr>
<td>Postoperative ileus (ref: no postoperative ileus)</td>
<td>0.254</td>
<td>1.29</td>
</tr>
<tr>
<td>Payment type (ref: retrospective)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>-0.039</td>
<td>0.96</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Gender (ref: female)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>-0.022</td>
<td>0.98</td>
</tr>
<tr>
<td>Race (ref: white)</td>
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<tr>
<td>African American</td>
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<tr>
<td>Hispanic</td>
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<td>1.14</td>
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<tr>
<td>Other</td>
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<td>1.01</td>
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<tr>
<td>APR risk of mortality (ref: Level 1)</td>
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<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>0.025</td>
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</tr>
<tr>
<td>Level 3</td>
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</tr>
<tr>
<td>Level 4</td>
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<td>APR severity level (ref: Level 1)</td>
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<tr>
<td>Level 2</td>
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<tr>
<td>Level 3</td>
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<td>Level 4</td>
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<td>Admission source (ref: physician referral)</td>
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<td>Admission type (ref: emergency)</td>
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<tr>
<td>Home health</td>
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<tr>
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</tr>
<tr>
<td>Other</td>
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<td>Hospital beds (ref: 100 or less)</td>
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<tr>
<td>201-300</td>
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<td>301-400</td>
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<td>1.08</td>
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<td>401-500</td>
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<td>1.09</td>
</tr>
<tr>
<td>Greater than 500</td>
<td>0.091</td>
<td>1.10</td>
</tr>
<tr>
<td>Hospital type (ref: rural)</td>
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<td></td>
</tr>
<tr>
<td>Urban</td>
<td>-0.033</td>
<td>0.97</td>
</tr>
<tr>
<td>Teaching (ref: nonteaching)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching</td>
<td>0.007</td>
<td>1.01</td>
</tr>
</tbody>
</table>


\(^b\)N = 17,896. Adjusted R-square = 0.5402, P < 0.001.

APR-DRG = All Patient Refined Diagnosis Related Group; ER = emergency room; HMO = health maintenance organization; ref = reference category.
capture the humanistic impact of postoperative ileus on patients, who experience pain and discomfort because of this condition. Lost work productivity due to prolonged hospitalization is another relevant component of indirect costs, which could be important from the perspectives of patients, employers, and society.

■ Conclusion

In patients who underwent colectomy surgery, postoperative ileus was associated with a 29% increase in hospital LOS and a 15% increase in hospitalization costs. Prevention of postoperative ileus could potentially yield benefits in reduction in hospital LOS and associated health care costs.

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DISCLOSURES

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Iyer and Saunders were responsible for concept and design, with the assistance of Stemkowski. Saunders performed the majority of data collection, with the assistance of the other authors. Iyer had primarily responsibility for data interpretation and writing of the manuscript, with the assistance of the other authors. Stemkowski and Iyer performed most of the manuscript revisions.

REFERENCES

Economic Burden of Postoperative Ileus Associated With Colectomy in the United States


We hypothesize that recent changes in policy and the spread of in-store medical clinics favor the provision of medication therapy management (MTM) services by large chain pharmacies while creating the potential for conflicts of interest from employed prescribers. First, MTM is now required by Medicare Part D, but the program may be more practical for community pharmacy chains than independent pharmacies. Second, in-store clinics have proliferated, which may accommodate the provision of MTM services in these community locations. Third, while physician ownership of pharmacies is restricted, the law has not anticipated the in-store clinic situations in which the pharmacy employs a prescriber on-site.

**Definition of MTM**

After the passage of MMA 2003, 11 national pharmacy organizations participated in a process to arrive at a consensus definition of MTM for the purposes of policy and rule making before the MTM billing codes were published. According to this definition, MTM includes a wide range of professional activities and responsibilities, such as (a) assessment of the patient's health status; (b) formulation of a medication treatment plan; (c) monitoring and evaluation of the therapy; (d) medication review to identify, resolve, and prevent medication-related problems; (e) recording of care delivered and communication with the patient's other primary care providers; (f) providing verbal education and training to the patient to promote appropriate medication use; and (g) providing information, support, and resources that enhance adherence to medications. In general, MTM services are intended to promote patient understanding about medication use, increase adherence to drug regimens, and detect drug-related problems. Studies of MTM interventions, such as the Asheville project and others, have demonstrated that MTM can effectively increase safety and reduce health care costs, decrease hospitalizations and lost work days, improve access to drugs, and reduce out-of-pocket costs. The evidence of the effects of clinical pharmacy interventions on health and on costs is mixed, with evidence demonstrating positive health outcomes but less evidence for medical cost savings or refill adherence. Results may be difficult to demonstrate because comprehensive MTM reviews require the cooperation of a physician or other prescriber in order to fully complete the health-medication intervention, although compliance issues can be resolved directly with the patient.

The American Medical Association Current Procedural Terminology (CPT) panel created 3 temporary CPT codes (0115T, 0116T, 0117T) for pharmacists and pharmacies providing face-to-face MTM services. These CPT codes, which became effective on January 1, 2006, allowed pharmacists to bill third-party payers for MTM services. On January 1, 2008, after only 2 years of use, the temporary codes were made permanent as CPT codes 99605, 99606, and 99607. The 99605 code is for a new patient, and 99606 is for a follow-up visit. These 2 codes are used for the first 15 minutes of time spent with a patient. If the visit extends for more than 15 minutes, then the code 99607 is used for each additional 15 minutes spent with the patient. Ostensibly, the pharmacist billing codes focus on the length of time spent in face-to-face contact with the patient and do not take into account the clinical complexity of the patient, unlike CPT codes used by physicians.

Medicare Part D MTM services are administered by the private PDPs and MA-PDs. Therefore, data from the billing codes will be held at the discretion of the private sector because MTM services are required for the contracts and are not billed to Medicare directly but, rather, are considered with administrative costs in the original bid. At present, the CPT codes will not provide an available source of government data on utilization of services...
by individual beneficiaries, although researchers with access to private data may choose to publish studies in the literature. Sponsors submit details to CMS in annual reviews but without separate tracking for MTM services.

Pharmacists are now able to obtain the National Provider Identification (NPI) number in order to seek reimbursement for services, although many pharmacists will continue to deal directly with plan sponsors and not with CMS. The MMA 2003 created the first reason for pharmacists to obtain an NPI; providers with an NPI, which is required by some but not all PDPs, are better able to contract with PDPs and bill for MTM. The list of providers with an NPI is searchable online at the National Plan and Provider Enumeration System (NPPES) website, https://nppes.cms.hhs.gov/NPPES/NPIRegistryHome.do. While pharmacists are identified as such, the NPI numbers cannot be sorted by profession.

Because the NPPES is a large dataset, we searched a small state for individual pharmacists with an NPI in May 2008. Our own state of Nevada has 2.5 million residents and about 2,000 licensed pharmacists and contains a large, fast-growing southwestern city in Las Vegas. We found that Nevada had at least 133 individual pharmacist health care providers that have obtained NPI numbers. Most of these, 110 (83%), are in Clark County, which contains Las Vegas and most of the state’s population. The NPI list included 61 providers with a doctor of pharmacy degree, 41 registered pharmacists, and 31 with other credentials, including students, science degrees, and none. The NPPES system indicated that 19 Nevada zip codes had more than 150 records (all providers), but a maximum of 150 records were displayed in search results, so the presence of additional providers in these areas (mostly in Las Vegas) is likely, but unknown.

**Part D MTM Providers: Suitable for Chain Stores**

Although utilization data are not freely available in the public sector, more details are known about the contracted PDPs and enrollment. In 2006, 20.7 million people were enrolled in Part D plans. In that year, a survey of insurance plans about MTM programs received responses from 70 companies operating 50 PDPs and 221 MA-PDs that represented 12.1 million enrollees in 21 distinct MTM programs. For contract year 2008, CMS announced there were 712 active Part D contracts with approved MTM programs, 609 MA-PD, and 103 PDP. These plans had various characteristics and rules, including the type of services provided and the eligibility requirements, all within the legal guidelines. A wide range of services was provided, including mailed information, telephone consultations, and in-person appointments. Eligibility requirements varied considerably, with 90.5% restricting enrollment based on number of disease states (median 3, range 2-5), 57.1% requiring a specific chronic condition, and 95.2% requiring a certain number of medications (median 6, range 2-24). According to CMS, algorithms are commonly used to identify beneficiaries for services that include reminders, letters, newsletters, and screenings—43% of MTM programs in 2008 used monthly algorithms, and 40% used quarterly algorithms.

Sponsor plans may or may not utilize community pharmacies for delivering services. The survey of plans found millions of enrollees, yet the actual amount of service provided was not enumerated in the report, and enrollees do not necessarily take advantage of MTM review opportunities. In addition, which health care professionals are providing which services is not clear. According to CMS, nearly one-half of plans in 2008 reported using in-house staff only for MTM services, whereas 28% used outside personnel, and 23% used a combination. Whether using in-house staff or outside contractors, 98.2% of PDPs and MA-PDs make use of pharmacists, whereas some Part D plans also use physicians (40.4%), nurses (50.7%), and other providers (32.4%) to deliver MTM services.

Pharmacists serving eligible patients in several plans, especially consultant pharmacists and those in independent community pharmacies, may encounter challenges in seeking reimbursement sufficient to cover costs. One report of a pilot project to provide telephonic MTM services concluded from the experience that “key components in MTM development and implementation include a dedicated clinical pharmacist, adequate documentation systems, and administrative support.” Therefore, possible barriers to utilization include high costs of providing services that are sometimes labor intensive, costs of acquiring new administrative capacity, and lack of training or an inability to provide the services. A small consultant pharmacy group that conducts MTM reviews at nursing homes under Medicare, for example, would have many challenges providing this service under Part D because of additional administrative personnel and, possibly, new information technology requirements to contract with and bill PDPs.

While implementing a new program is challenging to any existing operation, we argue that Part D arrangements are more practical for large chain community pharmacies that have infrastructure in place because of 3 obstacles: low reimbursement rates, additional billing systems, and need for clinical space and training. First, the reimbursement rate may be based on the face-time with patients, and an informal survey conducted by the Lewin Group found that the rate may be as low as $1 to $2 per minute, or approximately $75 to $120 for initial visits and $35 to $60 for follow-up visits. These rates are not sufficient to encourage and support the provision of MTM services, which are probably more feasible at a starting rate of $2 to $3 per minute. In contrast, the state of Minnesota has more satisfactory reimbursement for pharmacists providing MTM under Medicaid using a 5-step pay-scale that is not based solely on face-time but employs a more complicated formula that better includes a pharmacist’s expenses, such as number of therapy problems and time spent after the patient visit. A telephone-based MTM pilot project found that thorough reviews required 90 minutes each.
Second, many pharmacists do not have systems in place for billing plan sponsors. Depending on the plan sponsor, they may need to purchase software, obtain the NPI number, hire extra personnel, and submit forms correctly.21 Pharmacists will need to become familiar with specific billing key words and use the correct terminology in order not to have claims rejected.22 Third, some pharmacists do not feel prepared for consulting; many pharmacists need more training in MTM itself and may not have the space to conduct private consults.23-26 Many pharmacists are unfamiliar with billing as service providers, and most have not often been exposed to this concept in formal education or training.24,25 We suggest that these 3 obstacles make Part D MTM more attractive to large businesses, particularly if they have in-store clinical space and an existing billing infrastructure. An option for independent pharmacists is to join a network that provides administrative services, such as Outcomes Pharmaceutical Health Care which administers MTM programs nationwide.5 This enterprise started in Iowa in 1999 and assists with billing Medicare, insurance plans, and other payers who recognize the economic value of preventing medication errors and complications by providing MTM services. The company processed about 100,000 claims for MTM services in the 7 years from 2000 to 2006.5 In April 2009, the company website, http://www.getoutcomes.com/aspx/consumers/pharmacistfinder.aspx, listed 10,206 MTM locations, or “MTM Centers” in the United States and the District of Columbia, Puerto Rico, and the Virgin Islands. The website also lists locations for service in Canada and Central America. The state with the most Outcomes MTM Centers on this list was Florida (1,456), and high numbers were reported for Georgia (627) and North Carolina (590). These locations are often large chain pharmacies and grocery stores, such as at Walgreens, Rite Aid, Kroger, SafeWay, and Medicine Shoppe. Many Outcomes network providers that have undergone baseline training in MTM documentation and billing appear to be large chain community pharmacies, which suggests that large chain pharmacies have quickly prepared to deliver MTM services in response to the MTM opportunities available.

Role of In-Store Clinics in the Provision of MTM

While independent community pharmacists may not be particularly encouraged by the development of recent Medicare programs,26,27,28 larger community chain pharmacies appear to have an advantage in addition to larger scale. Informal discussions with local certified geriatric pharmacists suggested that a potential vehicle for Part D MTM delivery that would not face the same barriers encountered by independent pharmacies is the chain pharmacy in combination with the new in-store medical clinics. The 2006 survey of MA-PDs and PDPs found that 19% of plans, covering approximately 7.5 million enrollees, contracted out to community pharmacies for MTM services.16 An in-store clinic, also called a convenience care clinic, fits well with this MTM contracting model because it is usually a structure carved out of the store that provides “one-stop shopping” for health care.29 Typically staffed by licensed nurse practitioners and registered nurses, these clinics provide limited primary care services that are quick, inexpensive, and convenient to insured, underinsured, and uninsured individuals.30 Patients can have simple medical conditions diagnosed and prescriptions written and filled quickly.20,31 In theory, a pharmacist could see MTM clients in the clinical space, or MTM could be provided by another professional. Thus, this new in-store medical clinic model seems to be in a position to surmount barriers to offering MTM under Medicare. The clinics have low operational costs, appropriate space, and billing infrastructure.32 The MTM reimbursement rates would add beneficial profit-margin revenue to support compensation of a pharmacist or practitioner already working a shift in the clinic.

In-store medical clinics have proliferated, although growth has slowed recently.33 New clinics have opened in airports to meet the demand for travelers with chronic illness who cannot carry syringes that may be necessary for their medication because of heightened airport security and for airport employees who may require basic primary care services while at work.34 One 2007 study found 292 in-store clinics operated by 12 different companies/clinics in various chain stores across the country.31 According to our own search of company websites, 10 of the top 18 community pharmacy chains (determined by prescription sales figures)35 housed 973 in-store health clinics in February

### TABLE 1

<table>
<thead>
<tr>
<th>Pharmacy Store*</th>
<th>Clinic Name</th>
<th>Number of Locations</th>
<th>Number of States</th>
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</thead>
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<tr>
<td>CVS</td>
<td>Minute Clinic</td>
<td>545</td>
<td>24</td>
</tr>
<tr>
<td>Walgreens</td>
<td>Take Care Health Clinics</td>
<td>326</td>
<td>18</td>
</tr>
<tr>
<td>Target</td>
<td>Target Clinic</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Wal-Mart</td>
<td>Quickcare</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>HEB</td>
<td>RediClinics</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Medicine Shoppe</td>
<td>Corner Care Clinics</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Kroger</td>
<td>The Little Clinic</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Publix</td>
<td>The Little Clinic</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Longs</td>
<td>Quick Health</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Duane Reade</td>
<td>Walk-in Medical Care</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rite Aid</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Albertsons</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brooks-Eckerd</td>
<td>none (now Rite Aid)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SafeWay</td>
<td>none</td>
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<td>0</td>
</tr>
<tr>
<td>Ahold USA</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sears/Kmart</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Costco</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Winn-Dixie</td>
<td>none</td>
<td>0</td>
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</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>973</td>
<td></td>
</tr>
</tbody>
</table>

*Source: Drug Store News, August 22, 2005.35 Using this list of top chains, company websites of each chain were searched for information about numbers of in-store health clinics.
2009 (Table 1). CVS stores provide the most clinics, with 545 Minute Clinics in 24 states. Walgreens was second with 326 clinics in 18 states.

Employing a Prescriber: Potential Conflicts of Interest

The nurse practitioners and physician assistants who usually staff an in-store medical clinic are able to write prescriptions in most states. These prescriptions may be easily filled within the same community pharmacy, creating a potential conflict of interest. Even among the array of plans and pricing details, the prescriber may understand that some prescription or over-the-counter drugs are most profitable for the store. Indeed, a report of interviews with in-store clinic operators found that a major motivation to open a clinic was the potential for increased traffic to the pharmacy.

The American Medical Association has identified a potential conflict of interest concern with clinics located in pharmacies and other community stores. This recent trend presents a new “reversed ownership” scenario in which the pharmacies and community stores employ (in a sense “own”) the salaried nurse practitioner/prescriber. In health care, self-referral or referral-for-profit (referral by a provider to organizations in which the provider has a financial interest) has presented a situation in which financial interests may dilute quality of care and increase costs. Physician ownership of pharmacies was first restricted in 1989 under the first Ethics in Patient Referrals law sponsored by Representative Pete Stark (California), which proscribed patient referrals to a pharmacy owned by the physician. This law was updated in 1993, but evidence of over-utilization of services when financial incentives were present continued to emerge in certain areas of health care, such as radiology. The more specific and restrictive “Stark III” regulations were published in 2007.

However, the scenario of financial interests presented by in-store clinics has not been specifically anticipated by the rules. MTM reviews that occur in a clinic with a prescriber available may generate new prescriptions (or different, more profitable products) to be sold at the sales counter. Some in-store clinic patients could have particularly generous insurance that does not prevent steering them toward more costly products. Patients could also possibly be counseled to purchase medication when none would have sufficed. Or, the medication review could recommend replacing a prescription product with something available over-the-counter, which in some cases could boost store profits. Finally, because of economies of scale and ready availability of clinic space, large chain pharmacies that house in-store clinics operate at a competitive advantage over independent pharmacies in providing MTM.

Conclusion

The MMA 2003 mandate of MTM services within Part D plans will help further develop a practice that improves health, safety, and efficiency. These recent developments enhance the profession of pharmacy and its clinical cognitive services. The proximity of pharmacist and prescriber around an in-store clinic may even create a more desirable health care collaborative team approach, although more serious chronic conditions are not likely to be managed at a big retail store. At the same time, these trends have created a new and perhaps unanticipated conflict-of-interest situation to which the public sector should be alerted because large chain pharmacies now employ prescribers. In-store clinics have already attracted attention for possible conflicts of interest, but MTM services increase this potential because medication reviews may involve recommendations to make certain purchases. Meanwhile, at least 1 physician has responded to the proliferation of in-store clinics with a call for increased physician dispensing, without addressing the referral-for-profit problem.

With respect to program evaluation, the availability of billing codes for pharmacists providing MTM means that data on utilization may exist but are made public only at the discretion of private companies and not by CMS. Claims data from Medicare Part D, only recently made publicly available for research purposes, do not specifically enumerate MTM. Future research should include thorough assessment of data, reviews of MTM eligibility and enrollment protocols, analysis of pharmacists and other providers within and without the community pharmacy setting, and more assessment of outcomes and results from the programs. Because MTM is obligatory in PDP contracts and not specifically tracked, important public health data may be left uncollected.

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Cook had primary responsibility for concept and design and for revision of the manuscript. Mburia-Mwalili had primary responsibility for data collection. Data interpretation was performed by Cook, with assistance from Mburia-Mwalili. Writing of the manuscript was the responsibility of both authors.
Medication Therapy Management Favors Large Pharmacy Chains and Creates Potential Conflicts of Interest

REFERENCES


Still Looking for Health Outcomes in All the Wrong Places?
Misinterpreted Observational Evidence, Medication Adherence Promotion, and Value-Based Insurance Design

Kathleen A. Fairman, MA, and Frederic R. Curtiss, PhD, RPh, CEBS

Naturally, there is a strong desire to substitute intellectual capital for labor. That is why investigators often try to base causal inference on statistical models.¹

In his 1999 historical review of the often contentious debate over the distinction between mathematical association and causation, statistician David Freedman observed that using observational (nonexperimental) data to make accurate causal inference requires hard work, coupled with an uncompromising willingness to explore multiple explanations for relationships among natural phenomena. He cited the example of John Snow, a London physician who determined in 1855 that cholera was a waterborne infectious disease.

To reach his accurate conclusion, Snow performed a series of studies with a painstaking care that seems astonishing in light of today’s pressure to publish findings as quickly as possible when they have commercial or political value. Snow observed the relationship between the timing of sailors’ arrivals in London ports and contraction of the disease; described the case study of a man who contracted cholera shortly after occupying the apartment of an infected patient; mapped the locations of the victims, engaging in the meticulous work of tracing deaths to specific regions, apartment houses, and even to particular water pumps; and noted the absence of infection among employees of a local brewery who were permitted to drink the company product and “preferred ale to water.” Finally, he performed statistical analyses of mortality data for the years 1853-1854, comparing customers of the Lambeth water company, which in 1852 had moved its intake pipe upstream to a “relatively pure” water source, with customers of the Southwark and Vauxhall company, which continued to draw its water from the Thames River. History records Snow’s striking findings: The cholera death rates per 10,000 houses were 315 for Southwark and Vauxhall customers, 37 for Lambeth customers, and 59 for customers in the rest of London. A compelling case for a waterborne infectious agent was made.

What does it take to draw accurate causal inference from observational data? As Freedman observed, the process is complex. “[An] enormous investment of skill, intelligence and hard work seems to be a requirement. Many convergent lines of evidence must be developed. Natural variation needs to be identified and exploited. Data must be collected. Confounders need to be considered. Alternative explanations have to be exhaustively tested. Above all, the right question needs to be framed.”¹ To those who would argue that sophisticated statistical modeling obviates the need to consider confounding factors and alternative explanations when interpreting observational associations, Freedman’s answer was simple: “The technology is relatively easy to use. …. However, the appearance of methodological rigor can be deceptive.” More contemporary guidelines for research reporting acknowledge the same understanding: when interpreting associations, multivariate modeling is often appropriate and valuable, but is still potentially vulnerable to the effects of confounding and bias and is therefore no substitute for a randomized design.²³⁴

Lessons Learned From Confusing Association With Causation in Chasing Biomarkers

Curtiss and Fairman observed in the July/August 2008 issue of JMCP that “evidence-based” interventions targeted to biomarkers frequently do not produce the end point “outcomes we love,” such as reductions in hospitalization rates or mortality.² Notably, most of the instances cited were characterized by a single common pattern: the usurping of lower-quality evidence based on observational associations with higher-quality evidence garnered from experimental testing of hypothesized causal factors.

For example, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was conducted because observational research had documented associations of blood glucose and HbA1c (Alc) levels with cardiovascular events. Researchers randomized 11,140 patients with type 2 diabetes to standard glucose control or intensive glucose control, targeted to achieve an Alc level of 6.5% or less. During a median 5 years of follow-up, the patients randomized to the intensive glucose control intervention did not have a significantly lower risk of major macrovascular events (hazard ratio [HR] = 0.94, 95% confidence interval [CI] = 0.84-1.06), cardiovascular mortality (HR = 0.88, 95% CI = 0.74-1.04), or all-cause mortality (HR = 0.93, 95% CI = 0.83-1.06), but did have an increased risk of severe hypoglycemia (2.7% intensive control vs. 1.5% standard control; HR = 1.86, 95% CI = 1.42-2.40).⁵

Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was initiated because of high-quality prospective observational evidence suggesting that after “adjusting for other risk factors,” each 1% decrease in Alc was associated with a 21% decrease in the risk of diabetes-related mortality, a 14% decrease in the risk of cardiovascular mortality, and a 24% decrease in the risk of nonfatal myocardial infarction.⁶

²³⁴

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in the risk of all-cause mortality, and a 37% decrease in the risk of microvascular complications. ACCORD investigators randomized 10,251 patients to intensive therapy, targeted to achieve an A1c level below 6.0%, or standard therapy, targeted to achieve a level of 7.0%-7.9%. Contrary to observational evidence, treatment groups did not significantly differ on the primary study outcome, a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (HR = 0.90, 95% CI = 0.78-1.04). However, the intensive therapy group experienced significantly higher rates of hypoglycemia requiring medical assistance (10.5% vs. 3.5%, P < 0.001) and weight gain greater than 10 kilograms (27.8% vs. 14.1%, P < 0.001). More importantly, all-cause mortality rates were higher in the intensive-treatment than in the standard-treatment group (HR = 1.22, 95% CI = 1.01-1.46), prompting early termination of the trial by the National Institutes of Health after a mean of 3.5 years of follow-up.

Lessons Learned From the Medicare Health Support Experiment: Higher-Quality Evidence Contradicts Observational Studies of Disease Management

Sometimes the negative effects of misinterpreting observational evidence are only economic. For example, the proponents of widespread adoption of disease management programs by Medicare largely ignored the effects of selection bias (i.e., the attraction of health-conscious consumers to disease management programs) and regression to the mean (i.e., the statistical phenomenon in which higher-cost patients incur lower costs over time without any intervention) when interpreting observational associations between participation in disease management programs and positive outcomes. Disease management proponents were understandably unhappy and outspoken when the Congressional Budget Office announced in October 2004 that the evidence was insufficient to conclude that applying disease management programs (i.e., for congestive heart failure, coronary artery disease, and diabetes) in Medicare would reduce overall health spending. Proponents advocated for randomized trials of disease management interventions by Medicare as the path to show definitively that these interventions would simultaneously improve beneficiary health and reduce medical expenditures. But the evidence proved otherwise. The results of the much-anticipated Medicare Health Support (MHS) experiment, launched with its first randomization in August 2005, produced disappointment when researchers concluded in June 2007 that the cost of the MHS vendor fees had greatly exceeded medical savings, resulting in termination of the project.

Lessons Learned in Treatment Guideline Development

More seriously, the danger of confusing association with causation in establishing treatment guidelines and policies is a lesson learned many times over from the sometimes untoward experiences of patients whose providers relied on published observational research or on treatment guidelines that failed to account for quality of evidence. Today’s reputedly gold-standard protocols, if based on poor-quality evidence, can change unexpectedly tomorrow. Examples of widely respected treatment recommendations that were based on observational research, but subsequently called into question by more rigorous evaluation, include the use of hormone replacement therapy to reduce cardiovascular risk in postmenopausal women, influenza vaccination of persons aged 65 years or older to reduce mortality, and clinical protocols used in the treatment of patients with chronic kidney disease. “Although numerous observers have emphasized that clinical practice guidelines should not be translated into clinical performance measures in the absence of high-grade evidence supporting a relationship between the intervention and outcome,” Himmelfarb observed in 2007, “this is precisely what has transpired in the management of [end-stage renal disease].”

Confusing Association With Causation in Reporting the “Impact” of Medication Adherence on Health Outcomes

New evidence of hazards inherent in relying on observational evidence comes from an analysis conducted by Dormuth et al., who studied the relationship between adherence to statin therapy and positive health outcomes. Such studies of associations between medication adherence and various outcomes—including mortality, hospitalization, and health care expenditures—have become familiar fare to managed care decision makers. Typically consisting of retrospective analyses of administrative claims data, almost always with statistical adjustments for measured confounders, these studies routinely find that higher rates of medication adherence are associated with better outcomes and lower disease-related or all-cause health care cost.

These associations between adherence and improved health outcomes are often cited in assessments of various treatments that increase pharmacy benefit spending, such as newer products with less frequent dosing or fixed-dose single-pill combinations containing drugs available individually as generic drugs. The objective of this type of assessment is, of course, to suggest that if the payer is willing to adopt the new product, the increased prescription drug expense potentially could be partly or fully offset by reductions in total medical cost. Similarly, a recent “prescription for national healthcare reform” cited associations of adherence with lower total health care cost in making the case that $177 billion could be saved annually in the United States by improving adherence to prescribed medication and reducing medication-taking errors. Studies using observational designs and measuring associations are also cited by proponents of value-based insurance design (VBID) as evidence that copayment reductions, although increasing payer expenditures for prescription drugs, would improve medication adherence, which would presumably lead to health improvements and potentially to medical cost offsets.

These conclusions rely on a key assumption—that associations between medication adherence and positive health care outcomes...
represent cause-and-effect relationships that can be replicated through interventions targeted to the assumed causal factor, medication adherence. This key assumption is logically analogous to the hypotheses tested and refuted in the ADVANCE and ACCORD studies that interventions targeted to biomarkers, which are associated with clinical end points, would improve those end points in a cause-and-effect relationship.

New Evidence of the Hazards of Confusing Association With Causation: Adherence to Statins Reduces Workplace and Motor Vehicle Accidents

Dormuth et al’s study of medication adherence in 141,086 patients who were prescribed a statin for primary prevention provides new reason to be skeptical about the assumption that associations will consistently translate into effective interventions.19 Instead of studying the expected physiological outcomes of statin therapy, such as reduced rates of myocardial infarction or lower cardiovascular expenditures, Dormuth et al. assessed outcomes that are physiologically highly unlikely to be related to statin use. After statistically adjusting for confounders in a Cox regression analysis, using a method similar in approach to those used in other adherence studies,20-26,30,34,35 Dormuth et al. found that statin-adherent patients were less likely than nonadherent patients to have motor vehicle accidents (HR = 0.75, 95% CI = 0.72-0.79) or workplace accidents (HR = 0.77, 95% CI = 0.74-0.81) or to develop diseases unlikely to be related to the biological effects of a statin (HR = 0.87, 95% CI = 0.86-0.89). Statin-adherent patients were also more likely than nonadherent patients to use preventive screening services (HR = 1.17, 95% CI = 1.15-1.20).19

Dormuth et al.’s results provide new support for the hypothesis of the “healthy adherer effect,” a phenomenon “whereby adherence to drug therapy may be a surrogate marker for overall healthy behavior,” documented by Simpson et al. in a 2006 meta-analysis of 21 studies (46,847 subjects), of which 8 (19,633 subjects) were placebo controlled.36 Simpson et al. assessed the relationship between mortality and adherence for a variety of medications and disease states, such as beta blockers following myocardial infarction, antiretroviral therapy for human immunodeficiency virus infection, digoxin for heart failure, and statins for hypercholesterolemia. The studies had assessed adherence using a variety of measures that included patient self report, electronic drug monitoring, refill data, clinician estimates, and tablet counts. As expected, Simpson et al. found that good adherence (as compared with poor adherence) to “harmful drug therapy” nearly tripled the odds of mortality (OR = 2.90, 95% CI = 1.04-8.11). Odds of mortality were cut by approximately one-half for patients with good adherence to “beneficial drug therapy” (OR = 0.55, 95% CI = 0.49-0.62). However, Simpson et al.’s findings strongly suggested that these effects were not entirely attributable to the biological effect of the medication, since good adherence to placebo was associated with approximately the same mortality reduction (OR = 0.56, 95% CI = 0.43-0.74).36 Similar results were obtained in previous studies of propranolol, amiodarone, and candesartan, all of which found that adherence to either placebo or active drug therapy was associated with reduced risk of mortality.37-39

Quasi-Experimental Studies of Cost Sharing and Adherence: Better Guidance for Pharmacy Benefit Design

Providing another example of the hazards of confusing association with causation, well-designed quasi-experimental studies conducted in commercially insured populations have consistently shown, contrary to the findings of research conducted with less rigorous cross-sectional designs,36,39-41,46-48 that typical copayment increases (approximately $5 to $13) in commercially insured populations produce cost savings, especially for payer cost net of patient copay,41-45 with little effect on utilization overall,41-44 modest effect on total prescription drug expenditure41-45 and no effect on use of other medical services.43,44,46

Elasticity (price sensitivity) is remarkably low for prescription drugs, estimated at less than 0.2 in most analyses41 and just 0.1 in a 2007 panel data analysis of a large commercially insured sample (n = 17,798).37 Following copayment increases of up to $13, existing users of chronic medications, including antihypertensives and statins, do not discontinue therapy at higher rates compared with those experiencing no copayment change.41-44,46 Results for larger copayment increases are mixed. One study found higher discontinuation rates among users of proton pump inhibitors, antihypertensives, and statins following a change from a $7 to $30 copayment,41 but another study found price-inelastic response to copayment changes of $15-$25 among those with 2 or more claims for chronic medication in the 3 months prior to the cost-sharing increase.46,48

Greater sensitivity to cost sharing was exhibited in quasi-experimental studies of noncommercially insured, more vulnerable populations, such as elderly Medicaid enrollees with at least 8 claims per year for at least 3 chronic medication classes,49 Medicaid enrollees with schizophrenia,50 veterans with schizophrenia,51 and commercially insured groups that are subject to extreme and atypical copayment changes (e.g., a $23 increase from a single-tier plan at $7 to a $30 nonpreferred brand copayment).31 Unfortunately, studies of these atypical groups are often cited by VBID proponents as evidence of the harmful effects of cost sharing in commercially insured populations, despite clear lack of external validity (generalizability) in making the comparison.32,52

The few studies of cost-sharing decreases performed to date in commercially insured populations using quasi-experimental designs similarly suggest little price sensitivity. Karter et al. found that, despite an association between lower cost-sharing level and greater use of glucose testing strips among patients with diabetes, providing free testing strips shifted costs from patients to the payer without significant improvement in adherence to glucose testing protocols.53 Similarly, Sedjo and Cox, who used a difference-in-difference
design to compare matched cohorts of patients using brand simvastatin versus other brand statin medications before and after simvastatin’s patent expiration in June 2006, found only “modest” differences in medication possession ratio (MPR).54 Among brand simvastatin users (n = 13,319), who had experienced a copayment decrease upon patent expiration (from brand to generic copayment, reductions of up to approximately $20 depending on benefit design), adjusted mean MPR increased by an absolute (percentage point) 0.52%. Among users of other brands (n = 26,569), adjusted mean MPR decreased by 2.02%. The resulting difference of 2.54%, although statistically significant because of the extremely large sample size, represented a clinically unimportant 9.3 additional days of statin therapy per year. Elasticity was estimated at only 0.02, essentially no price sensitivity, for copayment reductions of more than $15.54

Chernew et al. produced a similar finding in a study of copayment decreases from $5/$25/$45 to $0/$12.50/$22.50 for generic drugs, preferred brand drugs, and nonpreferred brand drugs, respectively; the absolute (percentage point) MPR change for statins was 3.39%, representing a clinically unimportant 12.4 additional days of statin therapy annually.55,56 Results for antihypertensives (angiotensin-convverting enzyme inhibitors and angiotensin II receptor blockers), beta blockers, and diabetes drugs were similar at 9.5 to 14.7 days of therapy per year. Although noting a remarkable lack of transparency in the Chernew et al. study report, Fairman and Curtiss applied national data to its results and estimated that to achieve these tiny gains in adherence the annual per member per year (PMPY) intervention costs across the entire insured population would be large, $11.53, $9.10, and $18.60, respectively, for antihypertensives, diabetes drugs, and statins.56

Will Current VBID Research Provide Evidence That Payers Can Really Use?

A study currently in process, the MHealthy: Focus on Diabetes trial, is an observational difference-in-difference (interrupted time series) evaluation, comparing employees and dependents of the University of Michigan (n = 2,507), whose 3-tier copayments for selected chronic medications changed on July 1, 2006, from $7/$14/$24 to $0/$7/$18 (generic, preferred brand, and nonpreferred brand, respectively), with enrollees of the same managed employers.57 Medications targeted for copayment reductions include statins, antihypertensives, hypoglycemic medications, and antidepressants. Both the intervention and comparison groups meet the criterion for diabetes as defined by the study investigators, “at least 1 pharmacy claim for a hypoglycemic medication (oral, injectable, or inhaled) within the 12 months prior to the study timeframe.”57

The MHealthy study analysis plan was published in Implementation Science nearly 3 years after the start of the 30-month intervention. Currently, the analysis plan raises more questions than answers about the adequacy and transparency of this nonrandomized evaluation. First, key characteristics of the study groups, including the prescription drug cost-sharing amounts for the comparison group, the industry sector(s) for the comparison group, and the formular(ies) for both groups, were undisclosed. Also undisclosed were key features of the medical benefit, such as monthly premium; prior authorization requirements; and cost sharing for emergency room, inpatient, physician office visit, and preventive services.

This lack of disclosure is important because the MHealthy authors’ assessment of their design—“any change in the control group values may reflect naturally occurring changes over time … while any change in the [University of Michigan] intervention group will reflect both the same naturally occurring trends, as well as the impact of the value-based co-payment reductions”—may be inaccurate if the study groups are not comparable.58 When study groups in an interrupted time series design are not comparable at baseline, it is difficult to know what is “driving” differences in trend, especially if the groups respond differently to changes introduced simultaneously with the intervention.59 For example, university employees are not necessarily representative of employees in other industries in their responses to information, a particular problem in the MHealthy study because both the intervention and comparison groups received an educational letter “detailing the importance of medication adherence in diabetes” as part of the project’s implementation.57 Generally, the “natural” trends in health care utilization and expenditures for groups with different occupations, education, and income may diverge over time independent of any interventions.

Additionally, the MHealthy study plan indicates that the intervention and comparison groups are served by different pharmacy benefit management companies (PBMs),57 raising serious questions about whether services often routinely provided to clients by PBMs, such as newsletters, availability of mail order pharmacy, or other policies and services that are designed to influence prescription drug use, differ in ways that will affect study results. The use of different PBMs also amplifies concerns about the absence of formulary information in the analysis plan. Formulary differences in tier placement of drugs are critically important, and formulary differences can also include tier placement for newly approved brand drugs (tier 2, tier 3, or not covered), influencing trend change separate from the effect of the absolute copayment amounts. An additional confounder is the dissolution of the study’s managed care organization in a merger that took place in December 2007, 12 months before the study end date.59 Whether the intervention and comparison group employers made different systematic choices for their employees in response to this major change is both undisclosed in the MHealthy analysis plan and a potentially crucial determinant of between-group differences in trend.
Second, the generic dispensing ratio, a critically important measure of whether the copayment reduction influences members to use higher-cost brand medications in lieu of less expensive and therapeutically equivalent generic medications, is not listed as an outcome measure in the MHealthy study analysis plan. In previous quasi-experimental research, groups experiencing copayment increases were more likely to increase use of formulary brands and generic medications than were those experiencing no copayment change. Whether copayment decreases prompt the reverse response, cost-ineffective use, should have been an outcome measure in this study. The investigators do mention, as the sixth limitation described in the analysis plan report, an assessment of the “extent of tier-shifting” from lower-to-higher-tier drugs as “an empirical issue that we will explore,” but without describing any specific measures.

Third, the financial disclosures in the study implementation report do not mention that the Center for Value-Based Insurance Design at the University of Michigan, which employs 4 of the MHealthy investigators as faculty, is supported by 7 pharmaceutical manufacturers. Notably, the MHealthy financial disclosures also do not match those provided previously by several of the study authors in an April 2008 letter to the editor of JMCP on the topic of VBID. Thorough and accurate disclosure of financial relationships and other potential conflicts of interest would help readers and decision makers interpret the VBID and MHealthy study findings.

Illuminating Results From “Plausibility Calculators” for Medication Adherence Interventions
For the decision maker who seeks objective information in a world that is often long on claims of success and short on high-quality evidence, “plausibility calculators” are highly valuable tools, designed to help decision makers model the potential medical cost savings that could result from adherence promotion efforts. Following a concept originally advanced by the Disease Management Purchasing Consortium, plausibility calculators rely upon algorithms derived from published randomized controlled trials of the relationship between use of medications to treat chronic disease, such as statins and antidiabetic drugs, and adverse outcomes such as disease-related hospitalizations and emergency room visits.

Plausibility calculators for disease management and VBID are available online free of charge. Key assumptions, such as copayment reduction amounts for VBID programs and engagement rates (the percentage of patients who will be contacted) for disease management programs, are entered by users. Users can either enter hospitalization and emergency room utilization rates for their specific population or apply the rates pre-coded into the calculators based on published and nonpublished evidence. Instead of producing a single point estimate, the calculators produce ranges for various levels of key factors, such as adherence rate change, representing “what if” scenarios.

The results of plausibility calculators typically impose a sobering reduction on the sometimes overly enthusiastic estimates of medical cost offsets that are made by proponents of investments in disease management or reduction of prescription drug copayments. Generally, results suggest that to produce overall cost savings, interventions intended to promote adherence should (a) target only patients in whom previous high-quality research has demonstrated high risk of high-cost adverse events, and (b) provide copayment reductions solely or primarily for generic medications.

Association and Causation: Recommendations for Managed Care
What does evidence about association versus causation mean for managed care decision makers today? First, it strongly suggests that the purported outcomes of interventions to reduce or offset medical expenditures by increasing medication adherence should be viewed with healthy skepticism from a “caveat emptor” perspective if those interventions are supported primarily by observational data. To understand the potential harm in interpreting predictors as if they represented causal factors, an example presented by statistician Jane Miller is helpful: White hair and mortality rates may be highly correlated, “but that does not make white hair a cause of high mortality.” Just as managed care decision makers should not invest in hair coloration products to reduce mortality or in statin adherence promotion to reduce automobile accidents, they should not adopt medication adherence interventions that are based on low-quality observational data. Decision makers should judiciously target interventions to improve medication adherence in the high-risk patients who are most likely to benefit, using the most cost-effective medication to achieve the therapeutic goal and keeping in mind that the findings of “healthy adherer” studies suggest a limitation on the expected outcomes of interventions targeted to medication adherence.

Second, we should be reminded—again—of the importance of establishing a base of high-quality evidence for making decisions that affect the cost and quality of health care. Efforts to set system wide policy based primarily on observational evidence, such as those currently being made by proponents of the application of VBID to health care reform and Medicare Part D, should be addressed in a manner similar to what Centers for Medicare & Medicaid Services applied in the MHS—rigorous experimental testing and provision for early termination in the event of program failure. Confident projections should be replaced by evidence that is based on a randomized study design and reported transparently with complete financial disclosure by the authors. To do otherwise is to risk investing precious resources in interventions that, when put to the test of real-world use, do not work.
Still Looking for Health Outcomes in All the Wrong Places?

Misinterpreted Observational Evidence, Medication Adherence Promotion, and Value-Based Insurance Design

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58. Still Looking for Health Outcomes in All the Wrong Places? Misinterpreted Observational Evidence, Medication Adherence Promotion, and Value-Based Insurance Design
Adding Diagnosis Codes to Prescriptions: Lessons Learned From a Quality Improvement Project

The Centers for Medicare & Medicaid Services (CMS) provides coverage for prescription medications for Medicare beneficiaries through Parts B, C, and D, and has an interest in assuring the quality of the pharmacotherapy delivered to patients. After the implementation of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003), CMS requested that each one of its Quality Improvement Organization (QIO) contractors develop projects that might improve the quality of care delivered at the pharmacy. The Arizona QIO, Health Services Advisory Group, Inc. (HSAG), chose to implement a project that sought better communication between prescribers and pharmacists, proposing the inclusion of medical diagnoses, or International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes, on all prescription orders. A study in which pharmacists were given varying levels of information about hypothetical patients—ranging from only legally required information to complete details, such as medication profile, physician progress notes, and diagnosis—found that the more patient information pharmacists have the better able they are to identify problems with medication therapy. Based on this research, it was hypothesized that providing diagnostic information to pharmacists with prescriptions would enhance patient safety by (a) increasing dispensing accuracy (i.e., decreasing look alike/sound alike errors and handwriting misinterpretation), (b) helping pharmacists to target patient education, and (c) allowing for the identification of problems with prescribed therapy.

The project complements the current Arizona regulatory requirement that patient “problems,” or diagnoses, be tracked by pharmacists. The Arizona State Board of Pharmacy requires that a “problem list” be present in each patient profile in pharmacy computer systems. Although the presence of a problem list is rigorously enforced by compliance officers, neither pharmacists nor the state board can verify its accuracy; the problem lists are created through patient self-report or the pharmacist’s professional judgment based upon the therapy prescribed. To provide an effective health care process, accurate information is necessary. Because many medications may be used for several indications, the pharmacy problem list often includes inaccurate information.

Initially, this project was planned as a prospective, descriptive quality improvement project, using data provided by 2 pharmacy chains in northwestern and southeastern Phoenix, Arizona, over 2 time periods—January to May of 2005 (baseline), and January to May of 2007 (follow-up), thus allowing for the intervention of awareness-building regarding the importance of the diagnosis code on the prescription. Because the project was conducted by a QIO, it was deemed an “intrinsic part of normal health care operations” and therefore exempt from review by an Institutional Review Board. Representatives from participating pharmacy chains each recommended 12 physicians as potential project participants. Of 24 physicians, 2 (1 podiatrist, 1 family physician) agreed to include an ICD-9-CM code on each written or electronic prescription. Physicians were asked to use their current system of prescribing (handwriting, electronic, etc.) but simply add a description of the problem they were treating in either plain English or using an ICD-9-CM code. Pharmacists were asked to use those data to fill the prescription and to capture the data in their computer systems.

In the study pharmacies, the only centralized record is the pharmacy practice management software routinely used to conduct pharmacy business. In the case of one of the participating pharmacies, this proprietary software is the central data source for patient information (e.g., demographics, prescription usage, patient treatment preferences, and disease state/diagnosis code information). At the time of the project, the quality indicator was the percentage of prescriptions written or e-prescribed by participating physicians that included diagnosis codes, with a goal of 10% improvement from the baseline rate of 0%.

The number of prescriptions with a diagnosis code was expressed as a rate, defined as the number of prescriptions with a diagnosis code divided by the total number of prescriptions written. A total of 1,330 prescriptions were written by the 2 physicians and filled at the pharmacies during the follow-up period. One physician recorded ICD-9-CM diagnoses on 300 of 310 (97%) handwritten prescriptions but on none of 546 (0%) faxed prescriptions, for an overall rate of 35% during the follow-up period. The other physician, who wrote 474 prescriptions during the follow-up period, was not compliant. Despite volunteering initially, the physician did not provide diagnoses on prescriptions as requested. Although these results were suboptimal, much was learned from this project that may assist others in similar endeavors.

Barriers to Implementation of a Diagnostic Coding Program

Four main barriers to implementing the intervention were noted: (a) difficulty in recruiting physicians, (b) difficulty in recruiting pharmacies, (c) difficulty obtaining data from the information systems, and (d) funding changes.

Significant barriers arose while recruiting physician participants for the project. Specifically, physicians were worried that entering diagnosis codes on prescriptions could lead to denial of claims for “off-label” indications. Some physicians were so convinced that public and private payers might deny coverage for medications written off-label that they proposed writing only the labeled indication on the prescription regardless of the patient’s condition. Obviously, this behavior would not only have defeated the purpose of the project, but would have led to falsely “validated” data in the analysis of accuracy, which used the physician entries as a benchmark against which to compare the pharmacy data. These prescribers were not recruited to participate because of their concerns. Additionally, some prescribers were concerned that medical liability trial attorneys would view the availability of
diagnostic information as fodder for new cases. Many prescribers who were initially chosen for the recruitment process did not return phone calls from the lead pharmacist.

Recruitment of pharmacies was also an issue. Previously the collection and maintenance of diagnosis codes in pharmacy computer systems were performed to maintain compliance with a state regulation. Compliance officers randomly selected patient profiles to look for the presence of the problem list. However, the accuracy of the problem list was impossible to determine without access to the patient’s medical record. Thus, compliance officers had no way of determining whether the problem list was accurate, and the quality of the data maintained in the pharmacy problem list was not considered a priority for pharmacy providers. Diagnostic data were not typically mined or utilized internally due to their poor validity. As a result, pharmacies were reluctant to disclose data to the QIO despite the voluntary nature of the project because the poor quality of the data would have been revealed. Pharmacies were acutely aware of the limitations of their pharmacy data management systems, and most pharmacy providers respectfully declined to participate. More recently, we have learned that the pharmacies that declined to participate but now have knowledge of this type of project, have reviewed and updated their internal corporate policies to populate problem lists with more accurate entries. As a result of this project, pharmacy administrators at one of the study sites reported extensive changes to their policies and procedures. Among the changes made, the pharmacy has contacted the software vendor to request that ICD-9-CM codes be updated and pharmacists have requested that high-volume prescribers include diagnoses on the prescriptions to improve pharmaceutical care. Now that there may be a useful purpose for these data, such as analyses conducted on behalf of Medicare Part D or QIOs, several large pharmacy-chain organizations have decided to find ways to address the issue.

Pharmacy recruitment also suffered because pharmacies are new to the QIO program. Since pharmacies and pharmacists have never been considered “health care providers” by the Social Security Act and are acknowledged as providers only in the Medicare Part D benefit created by the MMA 2003, pharmacists and pharmacies had almost no knowledge of the QIO program prior to the CMS 2005–2008 QIO project cycle. Remedial education about the confidentiality and Health Insurance Portability and Accountability Act classification of the QIOs took many hours to communicate and will be an issue requiring additional effort as QIOs are directed to work more closely with retail and mail order pharmacies.

In addition, the pharmacies involved have had a difficult time mining the data in their systems, despite electronic pharmacy computer systems. Although pharmacies have an enormous amount of patient data, the pharmacy management systems are designed to retrieve the data 1 patient at a time, for the purpose of filling prescriptions and reviewing patient medication histories. Therefore, at the pharmacy level, mining population-level data for this project would have required dozens of staff hours, at considerable expense to the pharmacy providers. The lack of funding to defray project participation costs was also a significant barrier.

Although the QIO had wanted a larger sample size and greater participation from a broad range of prescribers and pharmacies, achieving this goal was difficult because during the recruitment phase of the project, CMS halted the project because of budget constraints. Originally, the QIOs were asked to work with the pharmacies and prescribers for a period of 12 to 18 months. At 6 months into the project, the QIOs were asked to suspend the project indefinitely as CMS reevaluated project funding priorities. As additional contract modifications were issued by CMS, study participants (prescribers and pharmacies), who had been providing unpaid assistance to CMS through the QIO, started to pull back their voluntary support. As the contract modifications changed the timing and project design, community partners lacked the personnel and financial resources to adapt their participation on a volunteer basis.

Problems in Accuracy of Diagnoses Entered on Prescriptions
In spite of these limitations, HSAG retrospectively examined the participating pharmacies’ databases for accuracy of diagnosis codes, comparing the data present in the pharmacy computers with the data provided by the physicians. HSAG received 1 dataset from each of the 2 participating pharmacies. Each dataset included all pharmacy claims data for patients aged 65 years or older for prescriptions written by each of the 2 participating physicians. The first dataset was obtained from the pharmacies in August 2005 and consisted of all paid claims with fill dates from January 2005 through May 2005. The second dataset was obtained from the pharmacies in August 2007 and consisted of all paid claims with fill dates from January 2007 through May 2007.

Additional technical issues associated with the pharmacy software were discovered during data analysis. A deficit in specificity of the ICD-9-CM codes present in the proprietary pharmacy practice software led pharmacy personnel to select the code in their system that most closely matched the code submitted by the physician. In some instances, the code was imprecise or inaccurate. In others, the pharmacy was unable to translate the ICD-9-CM codes at all. For example, a specific diagnosis such as benign renovascular hypertension (ICD-9-CM code 405.11) was not available among the choices pharmacists had in their computer systems. The available code selected by the pharmacist, 402.XX (hypertensive heart disease), was not the correct code in that it did not match the information provided by the physician. In addition, the only pain code available in one of the pharmacy systems was 307.81 (tension headache, incorrectly labeled by the pharmacy software as “pain”). This led all diagnoses related to pain, irrespective of body system, to be incorrectly categorized as tension headache. The proprietary software used by most pharmacies is able to upload all of the codes from the American
Medical Association (AMA) classification system, but has not had any call for such programming. The vendor has been asked by one of the participating pharmacies to expand its ICD-9-CM catalog, and has promised to comply on future software updates.

In addition, no matter what the mechanism for getting the prescription to the pharmacy—hand-written or faxed form—the participating pharmacies had to manually enter information from the prescriptions and their corresponding diagnoses into the pharmacy database. The only way to avoid the manual entry requirement is for true e-prescribing to occur. This did not occur with the participating physicians and pharmacies during this project.

As this project was implemented, an interesting disconnect in billing policies within CMS was noted. CMS currently requires prescribers and pharmacies transmitting outpatient prescriptions for Medicare Part B to include a diagnosis code on the face of the prescription and in the National Council for Prescription Drug Programs (NCPDP) standardized claim transmission field. Medicare requires pharmacies to collect diagnostic information for all claims submitted to Part B and determines which diagnosis codes are considered appropriate for payment of Part B-eligible medications. Medicare Part D does not have the same requirement. Pharmacists and physicians have been careful to note ICD-9-CM codes on oral chemotherapy prescriptions, diabetic testing supplies, and other durable medical equipment formulary items paid under the rules established for Part B. Future policy updates requiring the notation of an ICD-9-CM code on all Part D prescriptions may drive further improvement on a national basis.

Readers should recognize the careful balance between the needs of the health care payer and the fears of prescribers and pharmacies, striving for a system that promotes full disclosure and full exchange of information between health disciplines in a way that does not unfairly impede access to products even when used off-label. We recommend that the lessons learned in this project be taken into account when considering or designing a larger controlled study of the potential impact of including diagnosis codes with prescriptions on medication error rates.

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