

Persistence with Pharmacotherapy for Gastrointestinal Disease: Associated Costs of Health Care

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INTRODUCTION

During 1998, digestive diseases accounted for \$85.5 billion in total direct medical costs and \$22.8 billion in indirect costs.¹ In 1996, approximately 70 million people were affected by digestive diseases.² This translates to about 234,000 lives that are lost every year as a result of digestive illnesses.³ Digestive diseases account for 9% of all hospitalizations and 14% of all in-patient procedures.⁴ Incidence rates for specific illnesses are relatively high, estimated at 160 per 100,000 for infectious disease,² 8 per 100,000 for ulcerative colitis,⁵ and 7 per 100,000 for Crohn's disease.⁶

Pharmacotherapy for gastrointestinal (GI) diseases is costly. About \$138 million was spent on medications for ulcerative colitis in the U.S. during 1998.¹ More than \$10 billion per year is spent on proton pump inhibitors (PPIs) in the U.S. Furthermore, 23 drugs used for GI treatment made it to the top 200 generic drugs used in 2004.^{7,8} Advances in the treatment of inflammatory bowel disease (IBD) include delayed-release mesalamine (e.g., Pentasa, Shire), balsalazide disodium (Colazal, Salix), and olsalazine (Dipentum, Pfizer) for treating and maintaining remission of ulcerative colitis, and sulfasalazine (Azulfidine, Pfizer) for the treatment of bowel inflammation, diarrhea, rectal bleeding, and abdominal pain in patients with ulcerative colitis.^{9,10}

Many factors affect health outcomes and costs of treatment—among them, how patients comply with their therapy.^{11–13} Recent literature has emphasized the importance of adherence to therapy in general,¹⁴ especially for patients with digestive diseases.^{15–17} Although several studies in different therapeutic areas have shown evidence that adherence to therapy improves health care outcomes,¹⁸ only about a third of patients adhere to

their health care provider's recommendations.¹⁹

Although pharmacoepidemiologic research on adherence to GI pharmacotherapy is limited, a study by Kane et al. found that only 40% of patients with clinically quiescent ulcerative colitis adhered to their mesalamine therapy. "Adherence" was defined as the ratio of the sum of the day's supply to the length of therapy.²⁰ The major factors associated with non-adherence were the patient's sex, marital status, and concomitant medications. The quality of the physician-patient relationship was also an important factor associated with adherence to mesalamine therapy.²¹

Given the burden of non-adherence and non-persistence (i.e., not filling a prescription) with therapy for ulcerative colitis and the rising attention focused on health policy decision-makers to implement programs to decrease costs related to health care, our study's aim was to determine the association between persistence with GI pharmacotherapy (consisting of aminosaliclates) and health care costs from the payer's perspective.

METHODS

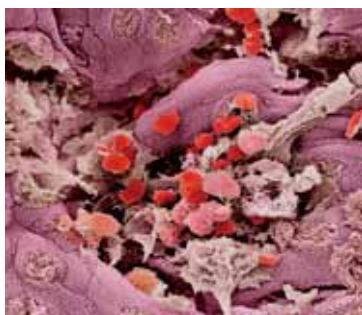
Population

The study population consisted of enrollees of Maryland CareFirst BlueCross BlueShield. About 3.6 million people (64% of the state's population) were privately insured in Maryland during the 2003–2004 period.²² A study conducted by Shaya et al. showed that approximately 29% of the non-elderly population covered by private insurance ranged in age from 45 to 64 years, whereas approximately 18% were under 18 years of age.²³ Approximately 58% of the population was female.

Study Sample

The study sample consisted of continuously enrolled patients in Maryland CareFirst BlueCross BlueShield with at least one month of follow-up who were prescribed at least one of the following aminosaliclate medications during the period from January 1, 2002, to December 31, 2004: balsalazide disodium, mesalamine, olsalazine sodium, and sulfasalazine. To increase the likelihood of including new users of the drugs of interest, we excluded from the sample any patients who used any of the

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Pharmacotherapy for Gastrointestinal Disease: Associated Costs of Health Care

four listed drugs during the first three months of the study period (from January 1, 2002, to March 31, 2002). Patients who started mesalamine therapy or corticosteroid enemas were also excluded because of the difference in administration technique, compared with oral medications, resulting in different paradigms of persistence with therapy.

Measurements of Persistence

Several methods can be used to measure adherence to medications; we chose the "persistence" measure because of its inherent advantages.²⁴ The pattern of patients who were prescribed aminosalicylates was classified as "discontinuation," "switching," or "persistence." The initial drug used (balsalazide disodium, delayed-release mesalamine, olsalazine sodium, or sulfasalazine) was labeled as the index drug and was flagged for each patient in the study.

We considered the date of the first claim for the index drug to be the index date. For each patient, we analyzed prescription claims records for continuity of consecutive refills of the index drug, within a margin equal to the total expected length of time until the next refill (the number of drug days supplied plus 15 days).

Patients were followed until they discontinued their medication, withdrew from the BlueCross BlueShield plan, or reached the end of the study period. Patients were assigned a "discontinued" status if the period between the last prescription they had and the new one was greater than the number of drug days supplied plus 15 days.

If patients filled a prescription for one of the drugs under study that differed from the index drug within 15 days after the prescription's expiration date (the number of drug days supplied plus 15), their status was classified as "switched."

If patients did not switch to another medication or if they discontinued the study drug after the first prescription, they were considered "persistent" until a "switching" or "discontinuation" pattern was identified.

If patients had no more claims in the enrollment period, if they withdrew from BlueCross BlueShield, or if they reached the end of the study period (December 31, 2004) with no discontinuation or switching, they were classified as persistent.

For the purpose of this study, switching to another drug was classified as "non-persistence" (defined as a failure to refill a prescription claim). To check for the robustness of our results, we conducted several sensitivity analyses in which switched patients were considered persistent; the refill grace period varied from 30 and 60 days, respectively, and the index drug was added as a covariate.

Statistical Analysis

We conducted a retrospective, longitudinal pharmacy and medical claims database analysis. Descriptive statistics were used to compare the baseline characteristics as well as the annual average costs of persistent versus non-persistent patients. Generalized linear models with a logarithmic link function and a gamma distribution were built to determine the association between annual average cost per patient, by type of health care service, and to determine persistence with aminosalicylate pharmacotherapy.

We adjusted the models for age, sex, and comorbidities by constructing a Charlson Comorbidity Index²⁵ using the approach suggested by Deyo et al.²⁶ Each category of services was subdivided into GI-related and non-GI-related, on the basis of the primary diagnosis (ICD-9 code) reported in each medical claim. SAS version 9.1 software (SAS Institute, Cary, NC) was used to perform all statistical analyses; tests of statistical significance referred to the 0.05 alpha level.

RESULTS

The inclusion and exclusion criteria resulted in a total of 4,313 patients in the index medication sample. Approximately 57% of the subjects were female, and 66% were 40 years of age and older, with an average age of 47.3 years (median, 47 years; standard deviation, 17 years). Nearly three quarters (74%) of these patients initiated therapy with delayed-release mesalamine; the remaining subjects began a regimen of sulfasalazine (16%), balsalazide (8%), or olsalazine (2%).

Persistence and Non-persistence

As shown in Table 1, 78% of the patients in the cohort were non-persistent with their index drug. The proportion of non-persistent patients taking the index drugs and in all age categories varied significantly (range, 74%–82% and 68%–80%, respectively). Patients younger than 18 years and those who began sulfasalazine therapy had the lowest persistence rate.

Unadjusted average annual costs for persistent and non-persistent patients are compared in Table 2. Non-persistent patients incurred significantly higher costs for admission, outpatient visits, and office visits compared with those who persisted with their medication. As a result, non-persistent patients incurred, on average, an additional cost of \$1,973 and \$1,875 in annual medical and total health care expenditures, respectively,

continued on page 663

Table 1 Baseline Patient Characteristics

| | Total | Persistent | | | |
|-------------------|-------|------------|-------------|-------|-------------|
| | | Yes | Percent (%) | No | Percent (%) |
| Total | 4,313 | 930 | 21.6 | 3,383 | 78.4 |
| Age* | | | | | |
| <18 years | 131 | 41 | 31.3 | 90 | 68.7 |
| 18–39 years | 1,344 | 274 | 20.4 | 1,070 | 79.6 |
| 40–64 years | 2,175 | 473 | 21.8 | 1,702 | 78.3 |
| 65+ years | 663 | 142 | 21.4 | 521 | 78.6 |
| Sex | | | | | |
| Female | 2,439 | 512 | 21 | 1,927 | 79 |
| Male | 1,874 | 418 | 22.3 | 1,456 | 77.7 |
| Index Drug* | | | | | |
| Balsalazide | 324 | 59 | 18.2 | 265 | 81.8 |
| Mesalamine | 3,193 | 673 | 21.1 | 2,520 | 78.9 |
| Olsalazine sodium | 101 | 22 | 21.8 | 79 | 78.2 |
| Sulfasalazine | 695 | 176 | 25.3 | 519 | 74.7 |

*The proportion of non-persistent patients varies significantly ($P < .05$) across the categories.

Pharmacotherapy for Gastrointestinal Disease: Associated Costs of Health Care

continued from page 658

Table 2 Unadjusted Annual Average Costs (in Dollars, \$)

| Type of Health Care Service | All Patients (N = 4,313) | Persistent | | Difference in Annual Average Cost |
|------------------------------|--------------------------|---------------|----------------|-----------------------------------|
| | | Yes (N = 930) | No (N = 3,383) | |
| Total | 5,626 | 4,155 | 6,030 | 1,875* |
| Pharmacy | 2,484 | 2,561 | 2,463 | -98 |
| Admission | 1,000 | 428 | 1,158 | 730* |
| Outpatient and office visits | 2,117 | 1,156 | 2,381 | 1,225* |
| Medical | 3,144 | 1,596 | 3,569 | 1,973* |

* P < .05.

Table 3 Association Between Persistence with Gastrointestinal Medications and Medical Costs

| Parameter | Estimate | P Value | 95% Confidence Interval | |
|----------------------------|----------|---------|-------------------------|-------------|
| | | | Lower Limit | Upper Limit |
| Male | -0.099 | .031 | -0.1902 | -0.0087 |
| Charlson Comorbidity Index | 0.428 | <.0001 | 0.3759 | 0.4808 |
| Age | -0.0132 | <.0001 | -0.0162 | -0.0102 |
| Persistent | -0.7855* | <.0001 | -0.8946 | -0.6764 |

* Compared with non-persistent patients, persistent patients incurred 54.41% lower mean medical costs.

Table 4 Association Between Persistence with Gastrointestinal Medications and Total Costs

| Parameter | Estimate | P Value | 95% Confidence Interval | |
|----------------------------|----------------------|---------|-------------------------|-------------|
| | | | Lower Limit | Upper Limit |
| Male | -0.0648 | .032 | -0.1242 | -0.0055 |
| Charlson Comorbidity Index | 0.3262 | <.0001 | 0.2934 | 0.359 |
| Age | -0.0038 | .0001 | -0.0058 | -0.0019 |
| Persistent | -0.3237 ^a | <.0001 | -0.3952 | -0.2522 |

^a Compared with non-persistent patients, persistent patients incurred 27.65% lower mean medical costs.

above that of the persistent patients.

General linear models were used to evaluate the association between persistence and costs after adjusting for age, sex, and comorbidities. As shown in Table 3, persistence with aminosaliclates was associated with lower mean medical costs.

For instance, after adjusting for confounding factors, mean medical costs incurred by persistent patients were 54.41% lower than mean medical costs incurred by patients who discontinued their therapy. Because persistent patients usually consume more medications, we investigated whether the increase in mean pharmacy costs resulting from persistence with therapy was offset by the decrease in mean medical costs by running the same

regression using total costs (instead of medical costs) as the dependent variable.

As shown in Table 4, mean total costs incurred by persistent patients were 27.65% lower than mean total costs incurred by non-persistent patients, after we adjusted for demographic variables and comorbidities. The results were not sensitive when we added the index drug as a covariate, when switched patients were considered persistent, and when we varied the definition of the refill grace period from 30 to 60 days, respectively. This suggests that our results were robust and not sensitive to changes in the assumptions of the model.

Comparison of GI-Related and Non-GI-Related Costs

Table 5 shows the results of the association of persistence with health care-related mean GI and non-GI costs by type of service. Mean pharmacy costs incurred by persistent patients were 6.93% higher than those incurred by non-persistent patients ($P = .1$). However, the increase in mean pharmacy costs was more than offset by the decrease in mean admission and outpatient and office visits, which led to markedly lower mean medical and total costs for persistent patients, when compared with those who discontinued their therapy.

In addition, the association of persistence with mean GI-related costs has a higher magnitude than that with mean non-GI-related costs. Indeed, mean GI-related admissions, as well as mean outpatient and office visit costs for those who persisted with aminosaliclate pharmacotherapy, were 78.81% and 53.60%, respectively, lower than the mean costs of those who did not persist.

In parallel, mean non-GI-related admission and outpatient and office visit costs were 61.90% and 47.51%, respectively, lower than the mean costs of those who discontinued their aminosaliclates.

DISCUSSION

Given the documented low rate of persistence among patients receiving GI pharmacotherapy, payers should be knowledgeable about the impact of persistence on total and medical costs. Our results demonstrated that patients who were persistent with aminosaliclates incurred significantly lower mean total and medical costs than patients who discontinued therapy. The magnitude of the impact was also higher for GI-related health care costs than for non-GI-related costs.

The results of our study of digestive disease are in agreement with other findings in different therapeutic areas. For instance,

Pharmacotherapy for Gastrointestinal Disease: Associated Costs of Health Care

Table 5 Association of Persistence with Gastrointestinal (GI) Medications with Costs by Type of Health Care Service

| Persistent vs. Non-Persistent Cost Comparison | Prescribed (%) | Admission (%) | Outpatient and Office Visits (%) |
|---|----------------|---------------|----------------------------------|
| GI-related cost | 20.80* | -78.81* | -53.60* |
| Non-GI-related cost | -1.57 | -61.90* | -47.51* |
| Total cost | 6.93† | -74.74* | -49.68*‡ |

Note: Results were adjusted for sex, age, and the Charlson Comorbidity Index.
 * $P < .05$
 † $P < .1$
 ‡ Interpretation: Compared with non-persistent patients, those who were persistent with GI medications incurred 49.68% lower mean outpatient and office visit costs.

a longitudinal cohort study of older diabetic patients by Balakrishnan et al. found that medication possession ratios were strongly associated with costs; higher ratios were associated with lower health care costs among diabetic patients.²⁷ Furthermore, studies have shown that poor adherence in patients with hypertension, hypercholesterolemia, and congestive heart failure was associated with higher health care costs, higher disease-specific costs, and higher use of health care resources, respectively.^{11-13,28}

Persistence rates in our study were lower than those found in the literature. Indeed, Kane et al. noted that 40% of the patients with quiescent ulcerative colitis were adherent to their therapy;²⁰ in our study, we found that only 22% were persistent with their index drug.

This difference in persistence rates can be explained through the variability of contributing factors in different settings and the application of different methodological approaches for estimating persistence rates. In fact, the Kane study recruited patients from the Gastroenterology Clinic at the University of Chicago; the median age of the patients was 42.5 years, and the proportion of males in the Kane cohort was 51%; in our study, the median age was 47 years and the proportion of males was 43%.

The difference in population baseline characteristics in our study and in the Kane study might have contributed to the difference in persistence rates; it is noteworthy that a patient's sex was a significant predictor of non-adherence in the Kane study. In addition, Kane et al. used the ratio of the sum of a day's supply to the sum of days in therapy as a measure of adherence; in our study, we used the time-to-refill approach, which is a more restrictive method for estimating persistence rates.

Other studies have used clinical markers and pill counts to measure adherence to GI pharmacotherapy. For example, van Hees and van Tongeren used the urine levels of serum sulfapyridine as an indicator of adherence to sulfasalazine in patients with inflammatory bowel disease after one to six months of their hospital discharge and in the outpatient setting.²⁹ Their findings confirm that the rate of non-adherence was roughly 41.2% in the first six months after hospital discharge and 12% after follow-up in the outpatient setting.

Riley et al. used pill counts and direct patient questioning to determine the adherence patterns (as well as other factors that might affect relapse) of patients with ulcerative colitis who

relapsed, compared with those who remained in remission.³⁰ The adherence rates discovered in their study were higher than 95% in both groups.

Higher costs among non-persistent patients were primarily a result of medical costs, mainly those related to admission and outpatient or office visits. The annual average costs in our study were relatively higher than the ones found in the literature.

Indeed, a study by Longstreth et al. found that the annual mean total cost for patients with irritable bowel syndrome was \$3,729;³¹ in our study, the annual average cost for a patient who received a prescription for an ulcerative colitis medication was

\$5,626. Although those two figures cannot be compared directly because of the difference in the characteristics of the diseases included in each pool, our estimate is still within a relatively conservative range.

Compared with the costs of other chronic diseases such as hypertension, total health care costs for patients using aminosaliculates were higher. A retrospective study at an internal medicine clinic found that the aggregate annual cost of laboratory, office visits, and medication used in treating a patient with hypertension was \$947 during the first year, \$575 in the second year, and \$420 after the second year, with about 80% of the total costs accounted for by medications.³²

The difference in costs for patients with hypertension and patients with GI illness might be a result of the type of health care services expenses that were included in the calculation of costs. For instance, in our study, calculated GI costs included expenses related to admissions; those costs were not included in the cost of treating hypertension. However, if 80% of the costs of treating hypertension are accounted for by the medication, then pharmacotherapy with aminosaliculates would still be more expensive than that used for hypertension, even after we accounted for inflation to convert the costs into 2004 dollars.

STUDY LIMITATIONS

Our study was a retrospective observational data analysis of pharmacy and medical claims. The major strength of claims analysis is that it permits the analysis of primary care data in real-life settings, as opposed to the highly controlled world of clinical trials. Although our study was unique in its approach in measuring persistence and estimating its impact on costs in a commercial population with GI diseases, we nonetheless acknowledge some limitations.

Because the data were extracted from a claims data set, they might not capture all episodes of care, specifically drugs that are obtained over the counter and bought without prescriptions; this might have led to an underestimation of health care costs. In addition, we could not determine which drugs were prescribed for off-label indications.

The data set used in our study did not contain information on race or clinical indicators that might be associated with health care costs such as smoking status and the body mass index (BMI).

Pharmacotherapy for Gastrointestinal Disease: Associated Costs of Health Care

Given the nature of retrospective claims data, we were unable to determine the reason behind switching; we therefore grouped patients who switched medications with the non-persistent group and ran a sensitivity analysis to check the robustness of our results. Patients might have switched medications because of poor response, side effects, allergies, or interactions with other concurrent drugs. Switching might also be an indicator of disease severity; however, we did adjust for comorbidities by using the Charlson Comorbidity Index.

There might have also been issues of external validity. Our study was based on data from Maryland CareFirst BlueCross BlueShield, and results might not be comparable to those of patients in Medicaid, Medicare, and other commercial plans in different states.

Another limitation arises from the application of the three-month window to increase the likelihood of including only subjects who had just started taking the drug of interest. Despite this exclusion criterion, the included patients might still have taken the index drug before January 1, 2002. It is also possible that a small group of patients receiving prior therapy could have slipped into the study sample when the plan had a benefit setting of a 90-day supply for maintenance medication.

CONCLUSION

Persistence with aminosalicylate therapy was associated with lower total costs and lower disease-specific costs. These important findings should be of interest to policymakers as they endeavor to evaluate programs that lead to lower monetary and economic costs. Future studies should explore factors that are associated with the likelihood of non-persistence and should explain how persistence with GI pharmacotherapy can reduce costs through better health care outcomes.

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