Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost

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Objective: The objective of this study was to evaluate the impact of medication adherence on healthcare utilization and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Research Design: The authors conducted a retrospective cohort observation of patients who were continuously enrolled in medical and prescription benefit plans from June 1997 through May 1999. Patients were identified for disease-specific analysis based on claims for outpatient, emergency room, or inpatient services during the first 12 months of the study. Using an integrated analysis of administrative claims data, medical and drug utilization were measured during the 12-month period after patient identification. Medication adherence was defined by days' supply of maintenance medications for each condition.

Patients: The study consisted of a population-based sample of 137,277 patients under age 65.

Measures: Disease-related and all-cause medical costs, drug costs, and hospitalization risk were measured. Using regression analysis, these measures were modeled at varying levels of medication adherence.

Results: For diabetes and hypercholesterolemia, a high level of medication adherence was associated with lower disease-related medical costs. For these conditions, higher medication costs were more than offset by medical cost reductions, producing a net reduction in overall healthcare costs. For diabetes, hypercholesterolemia, and hypertension, cost offsets were observed for all-cause medical costs at high levels of medication adherence. For all 4 conditions, hospitalization rates were significantly lower for patients with high medication adherence.

Conclusions: For some chronic conditions, increased drug utilization can provide a net economic return when it is driven by improved adherence with guidelines-based therapy.

Key Words: adherence, drug utilization, healthcare costs, hospitalization, pharmaceutical care

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Prescription drug expenditures are the fastest growing component of healthcare costs in the United States.[1,2] National outpatient drug spending has increased by 13% to 16% per year during the past few years,[2] and it is expected to continue to grow by 9% to 13% per year during the coming decade.[2] Much of the growth in drug spending is the result of increased use (more drugs prescribed for more people for more indications); this accounts for more than 50% of the growth in drug spending for many common conditions, including diabetes and hypercholesterolemia.[1,3] In an effort to manage this growth, health plan sponsors and plan managers have responded with a variety of programs aimed at containing utilization and cost. Some patients in prescription benefit plans have experienced higher copayments and tighter utilization controls, and physicians have been under increasing pressure to factor drug costs and coverage limits into their treatment decisions. All of the participants in the healthcare system face a common dilemma: are the benefits of prescription drugs worth the increased cost?

For many medical conditions, there is strong evidence that prescription drugs provide *clinical* value. Based on that evidence, pharmacotherapy has become an integral component of the treatment guidelines for many high-prevalence diseases, including diabetes,[4] hypertension,[5] hypercholesterolemia,[6] and congestive heart failure (CHF).[7] The more difficult question is whether prescription drugs provide net *economic* value to those who pay for health care. Does drug treatment reduce overall healthcare costs by reducing patients' need for expensive medical services such as hospitalization and emergency room (ER) treatment? Results of this kind have been demonstrated for several medical condi-

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tions.[8–13] For example, lipid-lowering drugs are generally cost-effective in secondary prevention of heart disease; by reducing the risk of cardiovascular events, they can produce a net return on investment.[10] This type of cost offset is a welcome benefit, but it may not be found for all high-prevalence conditions for which drug therapy is recommended. Some drug treatments may show a medical cost offset (in the short term or long term), and some may not show an offset at all.[14]

The therapeutic and economic benefits of drug treatment are often demonstrated in the controlled settings of clinical trials. These benefits may not be realized in day-to-day practice, especially for patients who are only partially compliant with their prescribed therapy. Adherence with medication therapy is generally low—approximately 50% to 65%, on average, for common chronic conditions such as hypertension and diabetes.[15,16] When conditions are treated suboptimally, symptoms and complications may worsen, leading to increased use of hospital and ER services, office visits, and other medical resources.[16,17] This suggests that higher levels of medication adherence may have positive economic value for some chronic conditions. Increased adherence may generate medical savings that more than offset the associated increases in drug costs. For some chronic conditions, there is evidence to support this hypothesis.[14,18–23]

There has been relatively little research assessing the cost impact of medication adherence for treatments provided under benefit plans in population-based settings. Some studies have assessed how healthcare costs are affected when patients reduce their drug use in response to coverage limits or copayment requirements. In a study of coverage limits in a Medicaid population, there was a net *increase* in total healthcare costs when patients were limited to a maximum of 3 prescriptions per month; many patients cut back on medications for chronic conditions (such as diabetes and CHF), and their use of medical services increased.[24,25] Medical utilization may also increase when patients cut back on drug use in response to copayment requirements.[26–29] These studies suggest that if patients' adherence levels drop as a result of benefit plan changes, medical utilization for some conditions may increase, and the increased medical costs may exceed the savings in drug costs.[14]

In this observational study, we evaluate the relationships among medication adherence, medical utilization, and healthcare cost in a large population of patients with combined benefit eligibility for prescription drugs and medical services. Drug cost, medical cost, and utilization are measured using pharmacy claims data and medical claims data, integrated at the patient level. After adjusting for age, comorbidity, and other factors, we estimate healthcare cost and hospitalization risk as a function of medication adherence. The analysis covers 4 high-prevalence conditions for which prescription drugs play a key role: diabetes, hypertension, hypercholesterolemia, and CHF. These conditions are generally chronic in presentation and often require long-term medication therapy.

METHODS

Study Population

Patients were participants in medical and drug benefit plans sponsored by a large manufacturing employer. Patients were initially identified for the study population if they had continuous medical and drug benefit eligibility during the period of the study, June 1997 through May 1999. Medical plan types included a health maintenance organization (HMO), a preferred provider organization (PPO), and a traditional fee-for-service (FFS) plan; participants in a small, capitated managed care plan were excluded because full medical cost data were not available at the patient level. Patients aged 65 and older (n = 73,997) were excluded because medical claims data were not available for their primary benefit plan (Medicare). A total of 137,277 patients (employees and dependents) met the inclusion criteria for the final study population. Age in the study population was distributed as follows: 0–18 (20.0%), 19–39 (16.0%), and 40–64 (64.0%). The population was 48.9% female and 51.1% male.

Medical data for the study population were drawn from an administrative claims database maintained by a health plan organization for all medical plan types. Drug utilization data were drawn from a prescription claims database maintained by Medco Health, the pharmacy benefits management company that manages the prescription benefit plan for this population.

Sample Selection

Separate study samples were drawn from the study population for purposes of analysis. A study sample was identified for each of the 4 conditions under study: diabetes, hypertension, hypercholesterolemia, and CHF. Patients were identified for a study sample if they used medical services for the condition and if they received prescription drugs for the condition. Patients were included in multiple study samples if they met the inclusion criteria for more than 1 of the medical conditions under study. Specific inclusion criteria were as follows.

Medical Claims

Patients were initially identified for a study sample if they received medical services for the condition during the first 12 months of the study period. To minimize false-positives, patients were identified for a study sample if they had 2 or more medical claims for outpatient services on different dates during the year, or if they had 1 or more claims for hospitalization or ER service during the year; outpatient services included physician office visits and outpatient de-

partment visits. For each medical condition under study, medical services were identified using primary and secondary International Classification of Diseases, 9th Revision (ICD-9) codes[30] in patients' claim records (Appendix).

Drug Claims

Patients were included in the final study sample if they received 1 or more prescriptions for the target condition during the 12 months after their first medical index claim (the first of 2 or more dates of outpatient service for the target condition, or the first of 1 or more dates of inpatient or ER service). The study did not include patients who were diagnosed with a condition but who were not using medications to treat it.

Data Collection

Utilization Data

Medical and drug claims were tracked concurrently during a 12-month analysis period for the patients in each study sample. For each patient, the analysis period began on the date of the first index claim, as defined previously.

Sociodemographic Data

Data on age, sex, employment group, and medical plan type were drawn from an eligibility database maintained by the health plan organization. Employment group was hourly or salaried (benefit plans differed for these 2 groups). Medical plan type was HMO, PPO, or FFS.

Adherence

Medication adherence was measured by patients' overall exposure to medications used to treat a given condition. Adherence was defined as the percentage of days during the analysis period that patients had a supply of *1 or more* maintenance medications for the condition (based on "days' supply" data in patients' prescription claim records). This measurement strategy reduces the risk of overestimating adherence (eg, in cases in which patients have overlapping prescriptions as a result of a change in therapy). For prescriptions extending beyond the end of the analysis period, days' supply was truncated at the end of the period. Patients in each study sample were stratified into 5 categories based on their adherence score: 1–19%, 20–39%, 40–59%, 60–79%, or 80–100%.

Comorbidity

Two comorbidity scores were derived for the patients in each study sample. The Charlson score was based on ICD-9 codes in patients' medical claims during the analysis period; it was computed using a Deyo-adapted Charlson scale.[31] A chronic disease index (CDI) was computed from patients' prescription claims during the analysis period. The CDI is a composite measure of drug use across a broad range of chronic conditions; a related index has been validated in previous studies.[32,33] For each analysis, the CDI score excluded the target medications for the condition under study; this precluded any confounding with the primary predictor of interest (medication adherence). The 2 comorbidity scores differ in their data source (medical vs. drug claims) and in the medical conditions they assess. The measures are positively correlated but not colinear. Significant positive correlations were observed for all 4 study samples ($r = 0.40$, diabetes; 0.42, hypertension; 0.38, hypercholesterolemia; 0.38, CHF; $P < 0.0001$).

Disease Subtype

For each target condition, specific ICD-9 codes were used as indicators of disease subtype. If any medical claim during the follow-up period contained 1 of these codes, the indicator was scored "1" for that patient; otherwise, it was scored "0". Scores were derived independently for each indicator.

Outcome Measures

The primary economic measures were total *medical costs* and *prescription drug costs* during the 12-month analysis period. Total *healthcare costs* were defined as the sum of medical costs and drug costs. Medical costs included outpatient services, ER services, and hospitalization; nursing home and home care services were not included. Drug costs included all ambulatory prescriptions (dispensed by outpatient, community-based, or mail-service pharmacies). Cost was defined as net cost to the plan sponsor; patient copayments and deductibles were not included.

Two types of cost were measured from the claims data: all-cause costs and disease-related costs. *All-cause costs* were medical or drug costs associated with *any* condition during the 12-month period. *Disease-related costs* were costs associated with treatment of the target condition; they were a subset of all-cause costs. For medical services, disease-related costs were identified by primary and secondary ICD-9 codes in medical claims data (Appendix). For hypertension and hypercholesterolemia, disease-related medical costs were identified by a broader set of cardiovascular codes that included common sequelae of the target condition (such as myocardial infarction or stroke). In many settings, these acute sequelae are more likely to be used for diagnostic coding, especially in cases of hospitalization or ER treatment. If claims analysis is restricted to diagnostic codes for the underlying condition (such as hypercholesterolemia), medical utilization and cost can be seriously underestimated. For drugs, disease-related costs were identified by drug classes in prescription claims data (Appendix).

The primary measure of medical utilization was *hospitalization risk*. This was defined as the probability of 1 or more hospitalizations during a 12-month period, expressed as

a percentage. Observed probability values were derived from medical claims data during the analysis period.

Data Analysis

We used multiple linear regression to evaluate the association between medication adherence and healthcare costs for each target condition. Cost estimates were adjusted for age, sex, comorbidity, disease subtype, employment group, and medical plan type. The following primary covariates were used in the regression model: age, sex, Charlson score, CDI score, employment group, PPO participation, HMO participation, and the ICD-9-based subtype indicators for the target condition. To adjust for possible nonlinearities in functional form, 3 interaction terms were used: age*age, age*sex, and CDI-score*sex. For each study sample, separate analyses were conducted for each category of cost (disease-related medical, disease-related drug, all-cause medical, and all-cause drug).

We used a logistic regression model to estimate the relationship between medication adherence and hospitalization risk for each target condition, adjusting for the same covariates as in the cost models described previously. For each condition, we estimated hospitalization risk as a function of adherence level.

Statistical Analysis

Overall fit of the regression models was tested using F-value and adjusted r-square (cost models) and Wald χ^2 (hospitalization models). Differences between adherence levels were evaluated for the 2 primary outcome measures: medical cost and hospitalization risk. The statistical significance of these differences was tested using 2-tailed t tests (medical cost) and χ^2 tests (hospitalization risk). The outcome for the highest adherence level (80–100%) was used as the reference for each pairwise comparison. Correlations among measures were evaluated using Pearson product moment correlation coefficients.

RESULTS

Patient Characteristics

The characteristics of patients in each study sample are shown in Table 1.

Disease-Related Measures

Estimated disease-related outcomes are shown in Table 2 for each target condition and adherence level. These estimates represent relative levels of cost and utilization after adjustment for all covariates.

Disease-Related Costs

For diabetes and hypercholesterolemia, high levels of medication adherence were associated with lower disease-related medical costs. These differences were statistically significant for most adherence levels when compared with the highest level of adherence ($P < 0.05$). For both of these conditions, *total* healthcare costs tended to decrease at high levels of medication adherence, despite the increased drug costs. For diabetes, disease-related healthcare costs decreased monotonically as a function of exposure to diabetes medications (Fig. 1). For hypercholesterolemia, healthcare costs were generally lowest for patients with 80% to 100% adherence, although the results were more variable than for diabetes. Medical costs for hypertension tended to be lowest at 80% to 100% adherence, but the differences were generally not significant. Differences for CHF were not significant.

Hospitalization Risk

For all 4 conditions, patients who maintained 80% to 100% medication adherence were significantly less likely to be hospitalized compared with patients with lower levels of adherence. These differences were statistically significant for most of the adherence levels tested ($P < 0.05$). For diabetes, there was a monotonic decrease in hospitalization risk as adherence to drug treatment increased (Fig. 1).

TABLE 1. Characteristics of Study Samples

Condition	Sample Size (n)	Mean Age (SD)	Percent Female	Mean Comorbidity Scores (SD)		Plan Type		Percent Salaried
				Charlson	CDI	Percent PPO	Percent HMO	
Diabetes	3260	53.9 (9.1)	45.4	4.4 (3.4)	0.6 (0.9)	10.0	11.0	32.3
Hypertension	7981	54.2 (7.7)	46.7	3.4 (2.9)	0.7 (1.0)	9.7	12.0	37.7
Hypercholesterolemia	2981	54.5 (7.5)	44.3	3.2 (2.9)	0.6 (0.9)	9.3	12.9	54.3
CHF	863	55.7 (7.9)	45.3	4.7 (3.1)	1.4 (1.2)	8.7	10.7	17.2

SD indicates standard deviation; CDI, chronic disease index; PPO, preferred provider organization; HMO, health maintenance organization; CHF, congestive heart failure.

TABLE 2. Disease-Related Healthcare Costs and Hospitalization Risk at Varying Levels of Medication Adherence

Condition	Adherence Level	N	Medical Cost ($)	Drug Cost ($)	Total Cost ($)	Hospitalization Risk (%)
Diabetes	1–19	182	8812*	55	8867	30*
	20–39	259	6959*	165	7124	26*
	40–59	419	6237*	285	6522	25*
	60–79	599	5887*	404	6291	20*
	80–100	1801	3808	763	4570	13
			F = 36.62†	**F = 88.57†**		**χ^2 (25 df) = 543.6†**
			Adj. r^2 = 0.18	**Adj. r^2 = 0.36**		
Hypertension	1–19	350	4847	31	4878	28*
	20–39	344	5973*	89	6062	24*
	40–59	562	5113	184	5297	24*
	60–79	921	4977	285	5262	20
	80–100	5804	4383	489	4871	19
			F = 46.44†	**F = 171.98†**		**χ^2 (31 df) = 1256.3†**
			Adj. r^2 = 0.13	**Adj. r^2 = 0.37**		
Hypercholesterolemia	1–19	167	6810*	78	6888	15*
	20–39	216	4786*	213	4999	13
	40–59	324	3452	373	3825	15*
	60–79	520	4938*	603	5541	14*
	80–100	1754	3124	801	3924	12
			F = 18.99†	**F = 320.08†**		**χ^2 (25 df) = 474.7†**
			Adj. r^2 = 0.10	**Adj. r^2 = 0.65**		
CHF	1–19	86	9826	15	9841	58
	20–39	70	7643	90	7733	63*
	40–59	82	11,244	134	11,378	65*
	60–79	107	13,766	158	13,924	64*
	80–100	518	12,261	437	12,698	57
			F = 5.33†	**F = 25.73†**		**χ^2 (24 df) = 169.7†**
			Adj. r^2 = 0.08	**Adj. r^2 = 0.34**		

*Indicates that the outcome is significantly higher than the outcome for the 80–100% adherence group ($P < 0.05$). Differences were tested for medical cost and hospitalization risk.

†$P < 0.0001$.

CHF indicates congestive heart failure.

All-Cause Measures

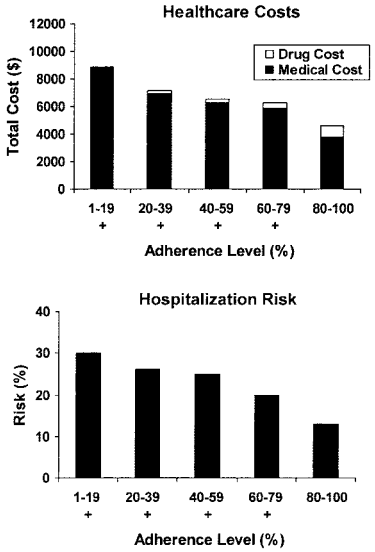
Estimated all-cause outcomes are shown in Table 3 for each target condition and adherence level.

All-Cause Costs

For diabetes, hypertension, and hypercholesterolemia, high levels of adherence with condition-specific drugs were associated with lower medical costs across *all* of the patients' treated conditions. These differences were statistically significant for most adherence levels ($P < 0.05$). For all 3 conditions, *total* healthcare costs tended to decrease at high levels of drug adherence, despite the increased drug costs. For diabetes, all-cause healthcare costs decreased monotonically with exposure to diabetes medications. Similar, although less uniform, patterns were observed for hypertension (Fig. 2) and hypercholesterolemia; healthcare costs were generally lowest for patients with 80% to 100% adherence. Differences for CHF were not significant.

Hospitalization Risk

For all 4 conditions, all-cause hospitalization rates were lowest for patients who had the highest level of medication adherence. These differences were statistically significant for all adherence levels ($P < 0.05$). For diabetes and hypertension, there was a monotonic decrease in hospitalization rates as medication adherence increased (Fig. 2, hypertension).



Estimated diabetes-related healthcare costs and hospitalization risk based on regression analyses. A plus sign (+) under a column denotes a value that is significantly higher than the outcome for the 80-100% adherence group ($P < 0.05$).

FIGURE 1. Diabetes: impact of medication adherence on disease-related healthcare costs and hospitalization risk.

Covariates

Cost and hospitalization risk showed significant positive associations with Charlson score and CDI score in most of the models tested ($P < 0.05$). Many of the disease subtype indicators also contributed significantly to model fit in these analyses. For most conditions, medical costs and hospitalization risk were significantly higher for hourly employees ($P < 0.05$). Age, sex, medical plan type, and the interaction terms generally had no effect on the outcome measures. CDI scores showed significant positive correlations with adherence (r = 0.15, diabetes; 0.28, hypertension; 0.16, hypercholesterolemia; 0.19, CHF; $P < 0.0001$). Correlations between Charlson scores and adherence were generally weak and nonsignificant (r = 0.00–0.07).

DISCUSSION

For diabetes and hypercholesterolemia, high levels of medication adherence are generally associated with a net economic benefit in disease-related costs. Higher drug costs are more than offset by reductions in medical costs, yielding a net reduction in overall healthcare costs. This pattern is observed at all adherence levels for diabetes and at most adherence levels for hypercholesterolemia. These results are consistent with earlier studies that have reported linkages between medication adherence and health outcomes for these conditions.[21,34–37] For hypertension, medical costs tended to be lowest at high levels of medication adherence, but offsets in total healthcare costs were generally not found. The cost impacts of adherence may be less salient for conditions like hypertension, for which a large fraction of the treated population has a relatively low risk of near-term complications.[14] No significant associations between cost and adherence were observed for CHF. Adherence-related differences in hospitalization risk were relatively small for these patients, and cost variability in the CHF study sample was exceptionally high.

To our knowledge, the current study is the first to demonstrate this pattern of cost offsets for diabetes and hypercholesterolemia in a large benefit plan population. Given the chronic nature of these conditions, it is likely that most patients in these study samples had been receiving medication treatment for an extended period before the analysis period began. The observed savings probably reflect the cumulative effects of adherence levels sustained over several years. Adherence rates in this study were typical of the rates often reported for chronic conditions.[15,16,34,38] Observed adherence rates (defined as the proportion of patients with 80–100% adherence) ranged between 55% and 73% for the 4 conditions in this study.

Although a formal cost–benefit analysis is not possible in an observational study of this type, the return on investment (ROI) can be estimated by comparing costs across adherence ranges (quintiles) in the disease-related analyses. For diabetes, the average incremental drug cost for a 20% increase in drug utilization is $177 and the associated disease-related medical cost reduction is $1251, for a net savings of $1074 per patient (an average ROI of 7.1:1). For cardiovascular conditions, the average ROI for a 20% increase in drug utilization is 4.0:1 (hypertension) and 5.1:1 (hypercholesterolemia). The results for diabetes (Fig. 1) suggest that there may be an inverse linear relationship between adherence and cost for some conditions; this should be tested systematically in future research.

Medication adherence is associated with net savings in *all-cause* healthcare costs for diabetes, hypertension, and hypercholesterolemia. For people with diabetes, all-cause medical costs decrease monotonically as adherence with hypoglycemic drugs increases. These savings probably reflect the effects of improved glycemic control on related conditions (such as microvascular disease and neuropathy), reducing the need for medical services.[39–42] Similarly, for the cardiovascular conditions, the cost offsets at high levels of medication adherence probably reflect the impact of cardiovascular medications on related conditions; for example, improved control of hypertension can slow the progression of renal disease.[5]

Adherence-based savings in medical costs appear to be driven primarily by reductions in hospitalization rates at higher levels of medication adherence. For all of the conditions studied here, hospitalization rates were lowest for patients who had high levels of adherence. Hospitalization is the largest component of medical costs in these study samples, so it is likely that the changes in hospitalization risk are the

TABLE 3. All-Cause Healthcare Costs and Hospitalization Risk at Varying Levels of Medication Adherence

Condition	Adherence Level	N	Medical Cost ($)	Drug Cost ($)	Total Cost ($)	Hospitalization Risk (%)
Diabetes	1–19	182	15,186*	1312	16,498	55*
	20–39	259	11,200*	1877	13,077	47*
	40–59	419	11,008*	1970	12,978	42*
	60–79	599	9363*	2121	11,484	39*
	80–100	1801	6377	2510	8886	30
			F = 51.33†	**F = 51.38†**		**χ^2 (25 df) = 695.3†**
			Adj. r^2 = 0.24	**Adj. r^2 = 0.24**		
Hypertension	1–19	350	8831*	916	9747	44*
	20–39	344	10,286*	952	11,238	39*
	40–59	562	8368*	1123	9491	36*
	60–79	921	7658	1271	8929	30*
	80–100	5804	6570	1817	8386	27
			F = 66.51†	**F = 50.94†**		**χ^2 (31 df) = 1573.2†**
			Adj. r^2 = 0.18	**Adj. r^2 = 0.14**		
Hypercholesterolemia	1–19	167	9849*	1067	10,916	26*
	20–39	216	6830*	1152	7982	18*
	40–59	324	5509*	1247	6756	20*
	60–79	520	6676*	1736	8412	21*
	80–100	1754	4780	1972	6752	16
			F = 22.37†	**F = 101.14†**		**χ^2 (25 df) = 500.7†**
			Adj. r^2 = 0.11	**Adj. r^2 = 0.37**		
CHF	1–19	86	22,003	1961	23,964	83*
	20–39	70	17,133	2055	19,188	81*
	40–59	82	24,103	2208	26,311	85*
	60–79	107	26,373	3412	29,785	84*
	80–100	518	19,056	3107	22,164	75
			F = 7.69†	**F = 11.71†**		**χ^2 (24 df) = 108.7†**
			Adj. r^2 = 0.12	**Adj. r^2 = 0.18**		

*Indicates that the outcome is significantly higher than the outcome for the 80–100% adherence group ($P < 0.05$). Differences were tested for medical cost and hospitalization risk.

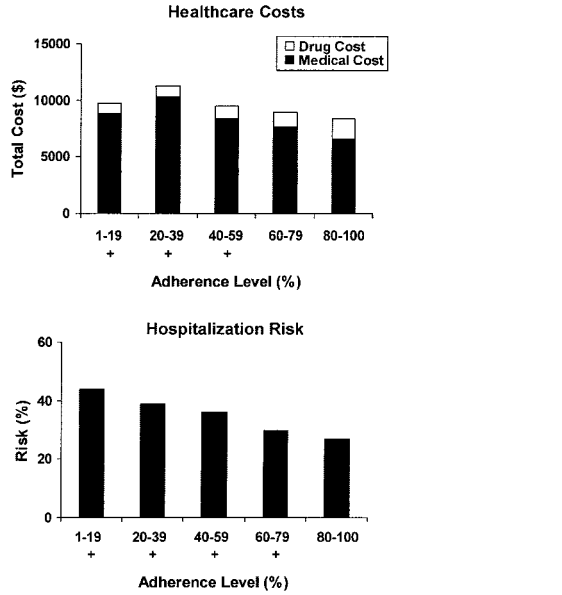
†$P < 0.0001$.

CHF indicates congestive heart failure.

primary driver of the cost savings observed at higher levels of adherence. This is consistent with results reported elsewhere on the impact of pharmacotherapy on hospitalization rates.[8,12,43,44]

This study was observational, so it is not possible to draw definite conclusions about the causal relationships among adherence, utilization, and cost. The cross-sectional nature of the design also poses some interpretive problems, because it yields some heterogeneity in the groups under study; for example, the "low-adherence" groups may include some patients who received short-term therapy or who started drug therapy late in the analysis period. However, given the chronic nature of the conditions under study, it is likely that most patients were continuing medication users (ie, it is likely that their treatment had started before the analysis period began). In cohort-based samples of patients with chronic conditions, most patients are prevalent (not incident) cases. The study can provide a good indication of the typical benefits of medication adherence in continuing patients with chronic disease. The study was not designed to track the time course of treatment of newly diagnosed patients, so it cannot define how quickly after the start of therapy the benefits of adherence begin to accrue.

The inclusion criteria for the study samples may limit the generalizability of the findings reported here. To reduce the risk of false-positives, at least 2 disease-specific claims were required when patients were identified based on outpatient claims. A single outpatient claim could indicate an office visit for evaluation; 2 claims are more likely to indicate a positive diagnosis. However, this selection methodology may



Estimated all-cause healthcare costs and hospitalization risk based on regression analyses. A plus sign (+) under a column denotes a value that is significantly higher than the outcome for the 80-100% adherence group ($P < 0.05$).

FIGURE 2. Hypertension: impact of medication adherence on all-cause healthcare costs and hospitalization risk.

produce a study sample that is weighted toward patients with more advanced disease or higher comorbidity, because it may exclude some patients who visit their doctors infrequently. A selection effect of this kind is suggested by the relatively high hospitalization rates for patients in these study samples; for example, the average all-cause hospitalization risk for the diabetes sample (35.9%) is higher than the rate reported in a study of primary care patients (21.1%).[45] The results of the current study are indicative of the adherence-related effects that may be expected for higher-cost patients with more advanced disease. Cost offsets may not be as prominent for healthier adults. Further research would be required to determine the applicability of the reported findings to other populations.

Each study sample included some patients who had more than 1 of the diseases under study. Including these patients makes the samples more representative, because combinations of these conditions (eg, diabetes and hypertension) are common. Excluding these patients would limit the external validity of the results. However, a consequence of including these patients is that the 4 study samples are not strictly independent. The samples provide 4 intersecting (but not fully independent) views of healthcare utilization in this benefit plan population.

There are some inherent risks to the use of medical claims data when measuring utilization and cost. In some cases, ICD-9 codes on medical claims may not accurately or completely reflect the patient's diagnosis. In the current study, medical chart data were not available to validate the coding on the medical claims.

The regression models used multiple covariates to control for the effects of comorbidity on utilization and cost. In most of the models, comorbidity was a significant predictor of utilization and cost. It is possible that unmeasured aspects of comorbidity risk could have biased the reported associations between adherence and cost. For example, if low-adherence patients tend to be sicker, then the costs at low adherence levels would be inflated if comorbidity is not adequately controlled. However, in this study population, there was a *positive* correlation between adherence and comorbidity (as measured by CDI scores)—the sicker patients tended to be more adherent. In this case, if comorbidity is not adequately controlled, it is more likely that the costs at *high* adherence levels will be overestimated. To the degree there is unmeasured comorbidity risk in this study, the models are likely to underestimate the cost reductions associated with high adherence.

CONCLUSION

Although the therapeutic benefits of pharmacotherapy are well understood, the potential economic returns are often missed in the public debate over rising prescription drug costs. Increased drug utilization can provide a net economic return when it is driven by improved adherence with guidelines-based therapy. Our results demonstrate that a net return may be obtained for 3 chronic conditions that account for a large share of long-term medication use—diabetes, hypertension, and hypercholesterolemia. Although drug costs are a relatively small fraction of total healthcare costs for these conditions, they have high leverage—a small increase in drug costs (associated with improved adherence) can produce a much larger reduction in medical costs. As more of these medications become available in generic form, their leverage will become even stronger; it will be possible to achieve the same therapeutic value and medical cost offset at a significantly lower drug cost. Because these benefits derive from improved adherence, greater attention should be devoted to educating patients on the value of their drug therapy and motivating behavior changes that improve adherence.

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APPENDIX Diagnostic Indicators and Drug Classes Used for Patient Identification and Claims Analysis

Condition	Patient Identification*	Disease Subtype Indicators*	Analysis of Medical Cost/Utilization*	Drug Classes
Diabetes	250.xx, 357.2, 362.0x, 366.41, 648.0	250.1–250.9	250.xx, 357.2, 362.0x, 366.41, 648.0	Insulins Oral hypoglycemics
Hypertension	401.xx–405.xx	401.x–405.x	401.xx–405.xx, 272.x, 410.xx–417.xx, 425.x, 428.xx, 429.0–429.3, 433.xx–438.xx, 440.x, 444.xx	Angiotensin-converting enzyme (ACE) inhibitors Angiotensin II receptor blockers Alpha blockers, beta blockers Calcium channel blockers Vasodilators Sympatholytic hypotensives Diuretics
Hypercholesterolemia	272.x	272.1–272.9	272.x, 401.xx–405.xx, 410.xx–417.xx, 425.x, 428.xx, 429.0–429.3, 433.xx–438.xx, 440.x, 444.xx	HMG CoA reductase inhibitors (statins) Fibrates Niacin preparations Bile salt sequestrants
CHF	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	402.x, 404.x, 428.0, 428.1, 428.9	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	ACE inhibitors Diuretics Digitalis glycosides Carvedilol

*ICD-9 codes (International Classification of Diseases—9th Revision).[30]
Where indicated, "x" takes any valid value.