

Binary Measures for Associating Medication Adherence and Healthcare Spending

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Prescription medicines are an important component in the treatment of diabetes and diabetes-related complications. When taken as directed, those medicines play a key role in slowing disease progression, preventing hospitalizations, and reducing premature mortality. Despite considerable evidence for the efficacy of medications in managing diabetes and other chronic diseases, it is estimated that patients never fill 20% to 30% of newly written prescriptions, and more than 50% of medications are not taken as prescribed.^{1,2} Improving adherence is critically important for reducing avoidable hospitalizations and preventing the use of costly acute care, but gaps persist in our knowledge about which patients should be targeted for intervention. In particular, we lack data about the specific patient populations in whom increasing adherence could have the greatest impact to improve outcomes and lower costs.^{3,4}

A substantial body of research demonstrates that adherence to medications used to prevent or manage diabetes and diabetes-related complications is associated with improved health outcomes and lower healthcare spending.⁵⁻¹³ To classify patients as adherent, researchers have typically used a cutoff of 80% for measurements of the medication possession ratio or proportion of days covered (PDC).^{12,14-16} This approach makes strong assumptions about the nature of the relationship between adherence and spending. These assumptions are typically treated as maintained rather than testable assumptions, and it remains unclear whether the functional form of this relationship is best characterized by a binary measure of adherence. A better understanding of the relationship between adherence and healthcare spending would help to inform stakeholders' expectations about the magnitude of spending reductions that are achievable through improvements in adherence. Additionally, it would assist payers and providers in identifying and targeting patients who are most likely to benefit from intervention.

METHODS

Data and Sample Selection

Our study used survey and claims data from the 2007 to 2010 Medicare Current Beneficiary Survey (MCBS), which is a nationally representative sample of Medicare beneficiaries. We limited our analysis to community-dwelling beneficiaries with diabetes who filled Part D–covered prescriptions for angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and were continuously enrolled in Medicare Parts A and B and a stand-alone Part D prescription drug plan for a full calendar year between 2007 and 2010. We classified beneficiaries as having diabetes if they self-reported having ever been given a diagnosis of diabetes by a physician. ACE inhibitors/ARBs were chosen for this analysis because they have been shown to be effective for the prevention of vascular complications in patients with diabetes and are recommended for virtually all elderly diabetics.¹⁷ Beneficiaries who received drug coverage through capitated Medicare Advantage plans were excluded because these plans do not generate the Parts A and B claims needed to evaluate medical spending.

Measures

Our dependent variable was total Medicare Parts A and B expenditures, adjusted to 2010 dollars using the all urban consumers component of the Consumer Price Index (CPI-U). To calculate adherence to ACE inhibitor/ARB therapy, we used the Part D prescription event data to determine the PDC, measured as a continuous variable ranging from 0 to 1. PDC is the adherence metric recommended by the Pharmacy Quality Alliance and is defined as the number of days a full supply of medication is on hand each month divided by the number of days in the month.¹⁸ Days spent in the hospital or a skilled nursing facility were excluded from both the numerator and de-

Take-Away Points

Patients are commonly considered to be adherent when they have medication on hand at least 80% of the time. We find evidence that a binary adherence measure may be insufficient to characterize the association between adherent behavior and Medicare spending due to nonlinearities in the adherence/spending relationship among Part D enrollees with diabetes.

- There is considerable heterogeneity in Medicare spending for beneficiaries above the conventional 80% adherence threshold.
- Part A spending is highest among beneficiaries at the top end of the adherence distribution.
- A better understanding of the adherence/spending relationship would assist stakeholders in targeting patients for adherence interventions.

nominator, as medications were presumably administered from facility supplies during inpatient stays.

Covariates in our regression analyses included sociodemographic characteristics, measures of health status, and controls for healthy adherer bias. Sociodemographic characteristics included age, gender, race and ethnicity, US Census region, and whether or not the beneficiary received the low-income subsidy. Health status was measured by: 1) a count of self-reported comorbid chronic conditions, including hypertension, hyperlipidemia, asthma/emphysema/chronic obstructive pulmonary disease, congestive heart failure, heart disease, osteoarthritis, and depression; 2) self-reported diabetes-related complications related to the eyes, feet, or kidneys; and 3) an indicator for whether the beneficiary originally qualified for Medicare on the basis of a disability.

Variables to control for potential healthy adherer bias included self-reported health status, the number of limitations in activities of daily living, any use of statins or oral antidiabetic medications, any insulin use, education level, marital status, and diabetes management behaviors including checking one's own blood sugar, checking for sores on feet, and having attended a diabetes management class. We hypothesized that beneficiaries who had more years of education, had spousal support, and took steps to actively manage their diabetes would be more likely to be engaged in their healthcare. If engaged beneficiaries were more likely to have both higher adherence and better overall health outcomes, this healthy adherer effect could confound the relationship between adherence and spending, thereby overestimating the impact of medication adherence.^{5,19-22}

Analytic Approach

To characterize the bivariate association between level of medication adherence and Medicare Parts A and B spending, we stratified the sample into quintiles based on the proportion of days covered. Due to the panel design

of the MCBS, beneficiaries could contribute multiple years of data to our pooled sample. This design violates a key assumption of many standard statistical analytic approaches—namely that the error terms across observations are independent and identically distributed. To account for correlation in the error terms, as well as the nonnormal and heavily right-skewed distribution of Medicare spending, we used cluster-robust generalized linear models with a gamma distribution and log link

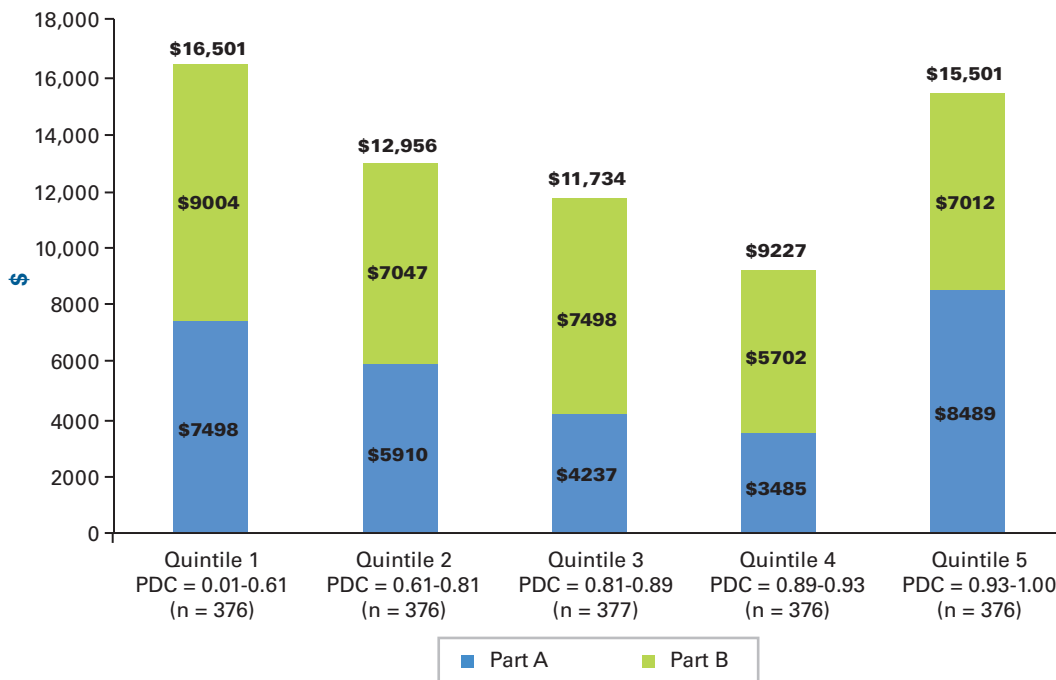
to estimate the relationship between adherence and total Medicare Parts A and B spending.²³ Robust standard errors were computed using an exchangeable correlation matrix.²⁴ Since virtually all beneficiaries in the sample (97%) had positive spending, we replaced the small share of observations with zero spending with a value of \$1. To more precisely investigate the functional form of the relationship between adherence and spending, we also performed multivariate regression using Part A spending and Part B spending as dependent variables in separate regression models.

We investigated nonlinearity in the relationship between adherence and spending using polynomial transformations of the continuous adherence measure. Tests for statistical significance on models including more than 1 polynomial function (eg, squared and cubed values) are subject to type II error due to the high correlation between the transformed variables. Orthogonal polynomials reduce the possibility of type II error by creating independent nonlinear functions of a given continuous variable in order to ensure that each transformed variable is evaluated individually without risk of unfounded correlation with other transformed variables. We used Hermite polynomials—part of the family of classical orthogonal polynomials—to develop nonlinear transformations of the PDC variable for inclusion in the regression models.²⁵ All analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina). The study was approved by the Institutional Review Board of the University of Maryland - Baltimore.

RESULTS

Application of our inclusion criteria resulted in a sample of 1881 ACE inhibitor/ARB users, 61.1% of whom met the conventional 80% threshold for adherence. The distribution of PDC was left-skewed, with an average of 77.2%, a median of 85.8%, and an interquartile range of 68.5% to 92.3%. After stratifying the sample by quintile of

■ **Figure.** Average Annual Medicare Parts A and B Spending by Quintiles of Medication Adherence^a



PDC indicates proportion of days covered.

^aMedication adherence is measured by the proportion of days covered.

PDC, each quintile contained 376 observations, except for the middle quintile, which contained 377 observations.

The unadjusted bivariate association between adherence and Medicare Parts A and B spending clearly suggests a nonlinear relationship (Figure). For total Parts A and B spending, increased adherence was associated with consistently lower spending across quintiles 1 through 4, reaching a turning point between quintiles 4 and 5. In quintile 5—which represents the most highly adherent beneficiaries—average total spending was considerably higher than for the rest of the sample, except for the least adherent beneficiaries in quintile 1. Although beneficiaries in quintiles 4 and 5 both meet the conventional definition of high adherence, we observed large spending differences between these groups. For instance, the average total spending for beneficiaries in quintile 4 was \$9,227 versus \$15,501 for those in quintile 5. Part A spending was also highest overall for quintile 5 (\$8,489)—more than double the amount for quintiles 3 (\$4,237) and 4 (\$3,485). We observed less overall variation in Part B spending across adherence quintiles, with no consistent pattern in the bivariate relationship between adherence and spending.

The Table summarizes the statistical significance and direction of the relationship between medication adherence and Medicare Parts A and B spending, adjusting for so-

ciodemographic characteristics, health status, and healthy adherer effects. Our interest is in the functional form of the relationship, and therefore, we focus here on the significance of the coefficients, rather than their magnitudes, and report the full regression results in an online eAppendix (available at www.ajmc.com). The statistical significance of the second- and third-order Hermite polynomials provides evidence for nonlinearities in the relationship between medication adherence and spending, but suggests a more complex nonlinear relationship than is reflected in the Figure. Specifically, the statistical significance of the third-order term suggests that the relationship is characterized by multiple inflection points. The results presented in the Table indicate that this relationship between adherence and Parts A and B spending appears to be entirely driven by Part A, as we did not observe a statistically significant association between adherence and Part B spending.

DISCUSSION

Consistent with the literature, we found evidence of a statistically significant association between Medicare spending and adherence to ACE inhibitor/ARB therapy among Part D enrollees with diabetes.^{5,9,12,13} Unlike prior studies, which have typically used a binary threshold to

■ **Table.** Adjusted Relationship Between Medication Adherence and Medicare Parts A and B Spending^a

Proportion of Days Covered (PDC)	Parts A and B Spending		Part A Spending Only		Part B Spending Only	
	Coefficient sign	P	Coefficient sign	P	Coefficient sign	P
H ₁ (PDC) ^b	+	.013	+	.008	+	.423
H ₂ (PDC) ^b	-	.012	-	.007	-	.394
H ₃ (PDC) ^b	+	.005	+	.003	+	.332

^aResults are based on regression models containing additional controls for age, race, gender, US Census region, receipt of the low-income subsidy, disability status at time of Medicare eligibility, number of comorbid conditions, diabetic complications, self-reported health status, number of activity of daily living limitations, education level, marital status, use of statins, use of oral antidiabetic medications, use of insulin, and diabetes self-management behaviors.

^bH_i(\cdot), where $i = 1, 2, 3$ represents Hermite polynomials; H₁(PDC) = 2(PDC); H₂(PDC) = 4(PDC)² - 2; H₃(PDC) = 8(PDC)³ - 12(PDC).

classify patients as adherent, we sought to better understand the functional form of the relationship between adherence and spending, and whether this relationship varied across the distribution of adherence. Our findings suggest that the relationship between medication adherence and Medicare spending is indeed nonlinear, and that binary measures of adherence are insufficient to fully characterize the relationship between adherent behavior and healthcare spending.

We observed considerable heterogeneity in average total spending for beneficiaries above the conventional 80% adherence threshold, including substantially higher total costs and Part A costs for beneficiaries with the highest levels of medication adherence. This heterogeneity suggests that there are important differences among beneficiaries commonly considered to be adherent. We also observed that the statistical significance of the relationship varied by type of Medicare spending, and that adherence had a much stronger association with Part A hospital spending than with outpatient and physician spending incurred under Part B.

On average, the most highly adherent beneficiaries incurred substantially higher Part A spending than their less-adherent counterparts. This should not and does not imply, however, that the relationship between good medication-taking behavior and poor health outcomes is a causal one. One possible explanation for this counterintuitive association is that highly adherent beneficiaries are further along in their disease progression. In this case, poor health status would increase beneficiaries' underlying risk of hospitalization, while simultaneously increasing their likelihood of adhering to therapy. Similarly, it may be the case that highly adherent beneficiaries experienced significant health shocks resulting in hospitalization early in the year, and improved the regularity of their medication-taking behavior following discharge. In this case, the high level of adherence observed for these beneficiaries would be the outcome, rather than the driver, of

high Medicare spending. Based on the current cross-sectional design, we cannot determine which case prevails. At the same time, our findings indicate that studies employing a cross-sectional design may miss opportunities to develop new insights into adherence and spending when an 80% cutoff is employed. Future adherence research employing longitudinal designs can build on the findings from this study to investigate the temporal relationship between adherence and spending, while accounting for nonlinearities in the relationship.

A few studies have challenged the use of an 80% adherence threshold, suggesting evidence of a broader dose-response relationship between adherence and outcomes. For example, Esposito and colleagues found evidence of a graded relationship between adherence and healthcare costs for patients with congestive heart failure, with spending rising monotonically as the level of adherence declined.¹⁵ Similarly, Briesacher and colleagues reported significant reductions in fracture risk and overall health costs associated with adherence levels as low as 40% for patients with osteoporosis, while Stuart and colleagues observed significant reductions in 3-year Medicare Parts A and B spending associated with adherence rates of 60% or higher for patients with diabetes taking ACE inhibitors/ARBs.^{12,16} In contrast, a recent study by Choudhry and colleagues found that patients with adherence levels below 80% did not experience the same significant reductions in adverse clinical events post myocardial infarction as did their more highly adherent counterparts.¹⁴

Limitations

An important limitation of our study was its small sample size, which limited the ability to investigate subgroup effects via interactions or defined subgroups. The reported results may mask differences between patient subgroups defined by demographic or clinical conditions. Future research with larger samples is necessary to confirm our findings and to explore whether the relationship between

adherence and spending varies across conditions and therapeutic classes. Indicators of patient participation in transitional care programs or other programs that directly support medication adherence are not available from this data set; however, participation in these programs may be correlated with underlying hospitalization risk.

CONCLUSIONS

This study makes an important contribution by highlighting the inadequacy of defining adherent behavior with a single cut point in some instances, a key assumption made in much of the existing adherence and cost-offsets literature. Our findings also reinforce the need for additional longitudinal research to determine the level of adherence necessary to achieve better health outcomes. Studies investigating the relationship between adherence and spending should build on a rich, nuanced conceptualization of the patient- and non-patient-level factors contributing to higher observed adherence. A better understanding of these relationships would assist policy makers, payers, and providers in identifying and targeting patients most likely to benefit from intervention.

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eAppendix Table. Beta Coefficients From Multivariable Regression of Medication Adherence on Medicare Parts A and B Spending

Independent Variables	Parts A and B Spending	Part A Spending Only	Part B Spending Only
<i>Proportion of days covered (PDC)</i>			
H ₁ (PDC) ^a	8.94 ^b	16.14 ^c	1.76
H ₂ (PDC) ^a	-3.31 ^b	-5.93 ^c	-0.69
H ₃ (PDC) ^a	1.08 ^c	1.92 ^c	0.23
<i>Sociodemographic characteristics</i>			
<i>Age</i>	0.00	0.01	0.00
<i>Census region</i>			
South	ref	ref	ref
Northeast	0.19	0.18	0.14
Midwest	0.06	-0.03	0.12
West	0.09	0.14	0.03
<i>Race/ethnicity</i>			
Non-Hispanic white	ref	ref	ref
Non-Hispanic black	0.19	0.11	0.24 ^b
Hispanic	0.44 ^b	-0.03	0.69 ^b
Other	-0.24	-0.66 ^b	0.08
<i>Female</i>	-0.09	-0.09	-0.10
<i>Low-income subsidy</i>	0.05	0.09	0.06
<i>Health status</i>			
<i>Number of comorbid conditions</i>	0.06	0.07	0.03
<i>Diabetic complication (eyes, feet, or kidneys)</i>	0.17	-0.01	0.28 ^c
<i>Medicare-eligible due to disability</i>	-0.17	0.00	-0.16
<i>Healthy adherer variables</i>			
<i>Number of activity of daily living limitations</i>	0.14 ^c	0.19 ^c	0.09 ^c
<i>Self-reported health status</i>			
Excellent/very good health	ref	ref	ref
Good health	0.20	0.31	0.10
Fair/poor health	0.43 ^c	0.59 ^c	0.32 ^c
<i>Statin use</i>	-0.01	0.02	-0.10
<i>Oral antidiabetic use</i>	-0.09	-0.15	-0.08
<i>Insulin use</i>	0.32 ^c	0.22	0.28 ^c
<i>Marital status</i>			
Married	ref	ref	ref
Single	0.20	0.29	0.08
Widowed	0.07	0.18	-0.05
<i>Education</i>			

Less than high school education	0.08	-0.17	-0.05
High school graduate	ref	ref	ref
At least some higher education	0.13	0.00	0.24 ^b
<i>Diabetes self-management behaviors</i>			
Checks own blood sugar	0.08	0.04	0.16
Checks feet for sores	-0.17	-0.18	-0.09
Ever attended diabetes management class	0.10	0.09	0.13

^a $H_i(\cdot)$, $i = 1, 2, 3$ represents Hermite polynomials; $H_1(\text{PDC}) = 2(\text{PDC})$, $H_2(\text{PDC}) = 4(\text{PDC})^2 - 2$, $H_3(\text{PDC}) = 8(\text{PDC})^3 - 12(\text{PDC})$.

^b $P < .05$.

^c $P < .01$.