

# Medication Nonadherence in Diabetes

## Longitudinal effects on costs and potential cost savings from improvement

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**OBJECTIVE**—To examine the longitudinal effects of medication nonadherence (MNA) on key costs and estimate potential savings from increased adherence using a novel methodology that accounts for shared correlation among cost categories.

**RESEARCH DESIGN AND METHODS**—Veterans with type 2 diabetes (740,195) were followed from January 2002 until death, loss to follow-up, or December 2006. A novel multivariate, generalized, linear, mixed modeling approach was used to assess the differential effect of MNA, defined as medication possession ratio (MPR)  $\geq 0.8$  on healthcare costs. A sensitivity analysis was performed to assess potential cost savings at different MNA levels using the Consumer Price Index to adjust estimates to 2012 dollar value.

**RESULTS**—Mean MPR for the full sample over 5 years was 0.78, with a mean of 0.93 for the adherent group and 0.58 for the MNA group. In fully adjusted models, all annual cost categories increased  $\sim 3\%$  per year ( $P = 0.001$ ) during the 5-year study time period. MNA was associated with a 37% lower pharmacy cost, 7% lower outpatient cost, and 41% higher inpatient cost. Based on sensitivity analyses, improving adherence in the MNA group would result in annual estimated cost savings ranging from  $\sim \$661$  million (MPR  $< 0.6$  vs.  $\geq 0.6$ ) to  $\sim \$1.16$  billion (MPR  $< 1$  vs. 1). Maximal incremental annual savings would occur by raising MPR from  $< 0.8$  to  $\geq 0.8$  ( $\$204,530,778$ ) among MNA subjects.

**CONCLUSIONS**—Aggressive strategies and policies are needed to achieve optimal medication adherence in diabetes. Such approaches may further the so-called “triple aim” of achieving better health, better quality care, and lower cost.

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Diabetes affects  $\sim 25$  million Americans, or 8.3% of the population, and it is a leading cause of heart disease, stroke, kidney failure, lower limb amputations, and blindness among U.S. adults (1). Estimated direct medical costs attributable to this disease were  $\$116$  billion in 2007, and the number of patients with diabetes will more than double by 2050 (2). Thus, diabetes is a highly prevalent disease that is important for both public health and public policy reasons.

Oral diabetes medications and insulin are cornerstones of diabetes management, yet up to one-third of diabetic patients may fail to derive optimal benefit from therapy because of medication nonadherence (MNA) (3–5). Indeed, diabetes medication adherence and hemoglobin A<sub>1c</sub> appear to be inversely related (5). More broadly, MNA has been estimated to occur in as many as 50% of chronic disease patients, resulting in  $> \$100$  billion spent each year on avoidable hospitalizations

(1,2). Multiple studies have also linked MNA with higher total diabetes-related, inpatient, and emergency department utilization and costs (6–8). For example, Lau and Nau (9) found that patients with good adherence ratios,  $\geq 80\%$ , had a 29% lower risk of hospitalization for any cause after adjusting for demographics, disease severity, and comorbid conditions. Similarly, Balkrishnan et al. (10) estimated that each 10% increase in medication adherence results in a mean decrease of 6.6% in all-cause hospitalizations.

Many medication adherence studies focused on cost are limited by small sample size, absence of precise adherence measures, or cross-sectional design. In addition, most analyses fail to appropriately account for the shared correlation among cost variables (11). To overcome these limitations and add to existing knowledge on the effects of MNA on cost, we used a multivariate, generalized, linear, mixed model (mGLMM) approach (which accounts for the shared correlation among cost variables) to estimate the inpatient, outpatient, and pharmacy-related costs in a longitudinal cohort of 740,195 U.S. veterans with type 2 diabetes. We also provide estimates of annual mean cost savings that might be obtained from potential increases in diabetes medication adherence in the veteran population.

## RESEARCH DESIGN AND METHODS

### Data source and sample

A national cohort of veterans with type 2 diabetes was created by linking patient and administrative files from the Veterans Health Administration (VHA) National Patient Care and Pharmacy Benefits Management databases. Veterans were included in the cohort if they had 1) type 2 diabetes defined by two or more ICD-9 codes for diabetes (250, 357.2, 362.0, and 366.41) in the previous 24 months (2000 and 2001), 2) ICD-9 codes for type 2 diabetes from inpatient stays and/or outpatient visits on separate days (excluding codes from laboratory tests and other nonclinician visits) in 2002, and 3) prescriptions for insulin or oral

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hypoglycemic agents in 2002 based on a previously validated algorithm (12). Veterans identified as having type 2 diabetes by ICD-9 codes were excluded from the cohort if they did not have prescriptions for diabetes medications in 2002 (see Supplementary Fig. 1 for details of cohort creation). The datasets were linked using patient scrambled social security numbers and resulted in 740,195 veterans who were followed until death, loss to follow-up, or December 2006. From this cohort, we calculated annual patient-specific VHA health care costs through VHA Decision Support System data, which extracts costs from the VHA payroll and general ledger. Costs were then classified into inpatient, outpatient (including emergency department), and pharmacy. The study was approved by our Institutional Review Board and local VHA Research and Development Committee.

### Study variables

The primary outcome variables were three cost types (pharmacy, inpatient, and outpatient) measured in 2006 U.S. dollars, and the perspective was that of the federal payer. VHA Decision Support System cost data were applied to encounter codes (diagnosis or procedure) from the VHA. VHA prescription drug costs were identified from the Pharmacy Benefits Management system and summed from the price per dispensed unit. Costs for each study year were represented in person-years to account for censoring.

Medication possession ratio is defined as the ratio of days for which a medication is supplied to the total days in a specified time interval. In this study, the medication possession ratio (MPR) was initially calculated in quarterly (90 days) intervals for both insulin and oral hypoglycemic agents for each patient (13). Subsequently, an annual average was calculated by taking the mean of the four quarterly MPR values in each year the patient was in the study from 2002 to 2006. If the MPR exceeded 1, the MPR was set to 1. An MPR value of 1 implies perfect medication adherence, whereas an MPR value of zero would imply that no medication had been taken. In general, MPR values of 0.8 are considered to imply good adherence (6,8). For example, Lau and Nau (9) found that patients with type 2 diabetes who did not obtain at least 80% of their oral hypoglycemic medications across 1 year were at higher risk of hospitalization in the following year.

Covariates included in the full model were age, sex, marital status, service-connected disability level, race/ethnicity, residence, region, and comorbidities. Marital status was defined as single or married. Service-connected disability level was categorized as <50 or  $\geq 50\%$ . Veterans with high levels of service-connected disability (i.e., >50%) are exempted from copayments. Race/ethnicity was classified as non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanic, and other/unknown/missing. Location of residence was defined as urban and rural/highly rural (14), and hospital region was defined by the five geographic regions of the country based on VHA Veterans Integrated Service Networks (VISNs): Northeast (VISNs 1, 2, and 3), Mid-Atlantic (VISNs 4, 5, 6, 9, and 10), South (VISNs 7, 8, 16, and 17), Midwest (VISNs 11, 12, 15, 19, and 23), and West (VISNs 18, 20, 21, and 22) (15).

Comorbidity variables included, anemia, cancer, cerebrovascular disease, congestive heart failure, cardiovascular disease, hypertension, hypothyroidism, liver disease, lung disease, fluid and electrolyte disorders, obesity, psychoses, and other (AIDS, rheumatoid arthritis, renal failure, peptic ulcer disease and bleeding, and weight loss) and were defined based on ICD-9 codes at entry into the cohort based on previously validated algorithms (15). In our final models, we included a categorical count of comorbidities defined as 0 = none, 1 = one, 2 = two, and 3 = three or more, a process that has been shown to be as or more efficient than more complicated algorithms (16).

### Statistical analyses

Descriptive measures, including mean and median costs, were computed for each cost type for each MNA group. Preliminary analysis included plotting the unadjusted mean costs in each cost type (inpatient, outpatient, and pharmacy) over time by MNA status, with time on the x-axis and unadjusted mean cost on the y-axis. The plots helped to examine trends over time in each source of cost by MNA status before adjusting for any other covariates. To model the relationship between the three cost categories and covariates, a joint model based on an mGLMM approach with shared random intercept was used (see Supplementary Data) (17).

Since the response variable is a vector of three correlated cost outcomes, mGLMM was implemented in SAS Proc

GLIMMIX (SAS Institute, Inc., Cary, NC). To account for the skewness in the observed cost data, a log-normal distribution with an identity link was used. Hence, the exponent of the parameter estimates can be interpreted as the percent change in each type of cost as a function of unit change in the covariates. Comparison with analysis results based on the assumption of a  $\gamma$  distribution and with results obtained by fitting separate models for each outcome was also performed (results not shown due to space limitations). In the joint models, the random intercept shared by the three cost outcomes captures the association in the natural heterogeneity among the individual subjects' baseline inpatient, outpatient, and pharmacy costs. Goodness of fit of models was assessed using pseudo-AIC (Akaike's Information Criterion)-type statistics and residual plots.

Potential savings to the VHA were estimated by examining the adjusted mean cost differential between adherent and MNA veterans based on various MPR cutoff values (0.6, 0.7, 0.8, 0.9, and 1) in every cost category in every year and multiplying by the number of MNA veterans in that year. Finally, projected annual potential total and incremental savings to the VHA at each MPR value was estimated using the 5-year mean MPR. The U.S. Department of Labor Statistics estimate of the medical component of the Consumer Price Index was used to convert all 2002–2005 costs to 2006 dollars prior to model estimation. The Consumer Price Index was also used to convert potential savings to the VHA from increased adherence from 2006 dollars to 17 February 2012 dollar values. All statistical analyses were performed using SAS 9.2 (SAS Institute, Inc.).

## RESULTS

### Characteristics of veterans with type 2 diabetes from 2002 to 2006

The final study sample consisted of 740,195 veterans with a diagnosis of type 2 diabetes during 2002 and who were followed until death, loss to follow-up, or through 2006. Ninety-eight percent were male, with a mean age of  $65.6 \pm 11.1$  years. Sixty-nine percent were NHW, 12.4% NHB, and 6.1% Hispanic, and 12.5% were another race or did not have race/ethnicity identified. Sixty-six percent were married, and 38.7% resided in a rural area. Geographically, 15.1%

lived in the West, 11.2% in the Northeast, 30.0% in the South, and 20.9% in the Midwest. Approximately twenty-six percent of subjects had a level of service-connected disability of >50%, qualifying them for exemption from pharmacy copayments. Fifty-seven percent had no comorbid illnesses other than diabetes, and 28.2% had one comorbidity, 10.8% had two comorbidities, and 4.5% had three or more comorbidities.

### Demographic characteristics and comorbidities by MNA status

Table 1 highlights significant differences between adherent and MNA patients with regard to demographic characteristics. Overall, ~42.3% of veterans were MNA. Compared with adherent subjects, the MNA group had a much lower mean MPR (57.7%) than the adherent group (93.1%), were older (65.9 vs. 65.4 years of age,  $P < 0.0001$ ), less likely to be male (97.5 vs. 98.0%,  $P < 0.0001$ ), and less likely to be married (61.7 vs. 68.2%). Based on available race/ethnicity

information, a higher proportion of subjects in the MNA group were NHB (15.4 vs. 10.2%) or Hispanic (7.0 vs. 5.4%). MNA patients also had a lower percentage of rural dwelling (35.6 vs. 41.0%) and a higher percentage of veterans living in the West (15.8 vs. 14.6%), Northeast (11.8 vs. 10.8%), and South (30.9 vs. 29.3%). Finally, the MNA group had a lower percentage of veterans with no recorded comorbidities (52.8 vs. 59.2%), but a higher percentage of one (28.9 vs. 27.7%), two (12.4 vs. 9.6%), and three or more comorbidities (5.9 vs. 3.5%).

### Mean unadjusted costs by MNA status

Figure 1 shows unadjusted means for each cost category by year and MNA status. Mean unadjusted pharmacy costs were lower for MNA veterans in every year, ranging from \$970 in 2002 to \$1,131 in 2006, relative to adherent veterans, ranging from \$1,671 in 2002 to \$1,762 in 2006. Mean unadjusted inpatient costs were higher for MNA veterans

in every year, ranging from \$13,105 in 2002 to \$15,337 in 2006, relative to adherent veterans, ranging from \$9,581 in 2002 to \$10,138 in 2006. Mean unadjusted outpatient costs were lower for MNA veterans (\$3,220 in 2002), until they became higher in 2005, with a value of \$3,762, relative to adherent veterans, with a value of \$3,546 in 2002 and \$3,751 in 2005.

### Longitudinal cost associations with MNA status

Table 2 highlights findings of significant ( $P < 0.001$ ) cost associations with MNA status among veterans with type 2 diabetes between 2002 and 2006 after adjustment for demographics and comorbidities and accounting for the correlation of cost categories over time. Relative to the adherent group, MNA was associated with a 37% lower pharmacy cost, 7% lower outpatient cost, and 41% higher inpatient cost between 2002 and 2006.

### Estimates of potential VHA savings from adherence at various MPR levels

Estimates of potential VHA savings from adherence at various MPR levels based on 17 February 2012 value dollars are shown in Table 3. Over the 5-year period, estimated annual potential savings were \$1,158,009,119 at MPR = 1, \$1,133,510,744 at MPR  $\geq 0.9$ , \$993,679,348 at MPR  $\geq 0.8$ , \$789,148,570 at MPR  $\geq 0.7$ , and \$661,529,175 at MPR  $\geq 0.6$ . Estimated annual incremental cost savings ranged between \$127,619,395 (from MPR = 0.6 to 0.7) and \$1,158,009,119 (from MPR = 0.9 to 1.0). Cost savings would be optimized at improvement from MPR = 0.7 to  $\geq 0.8$  (\$204,530,778), and adherence levels  $>0.8$  would lead to diminishing returns in terms of cost savings.

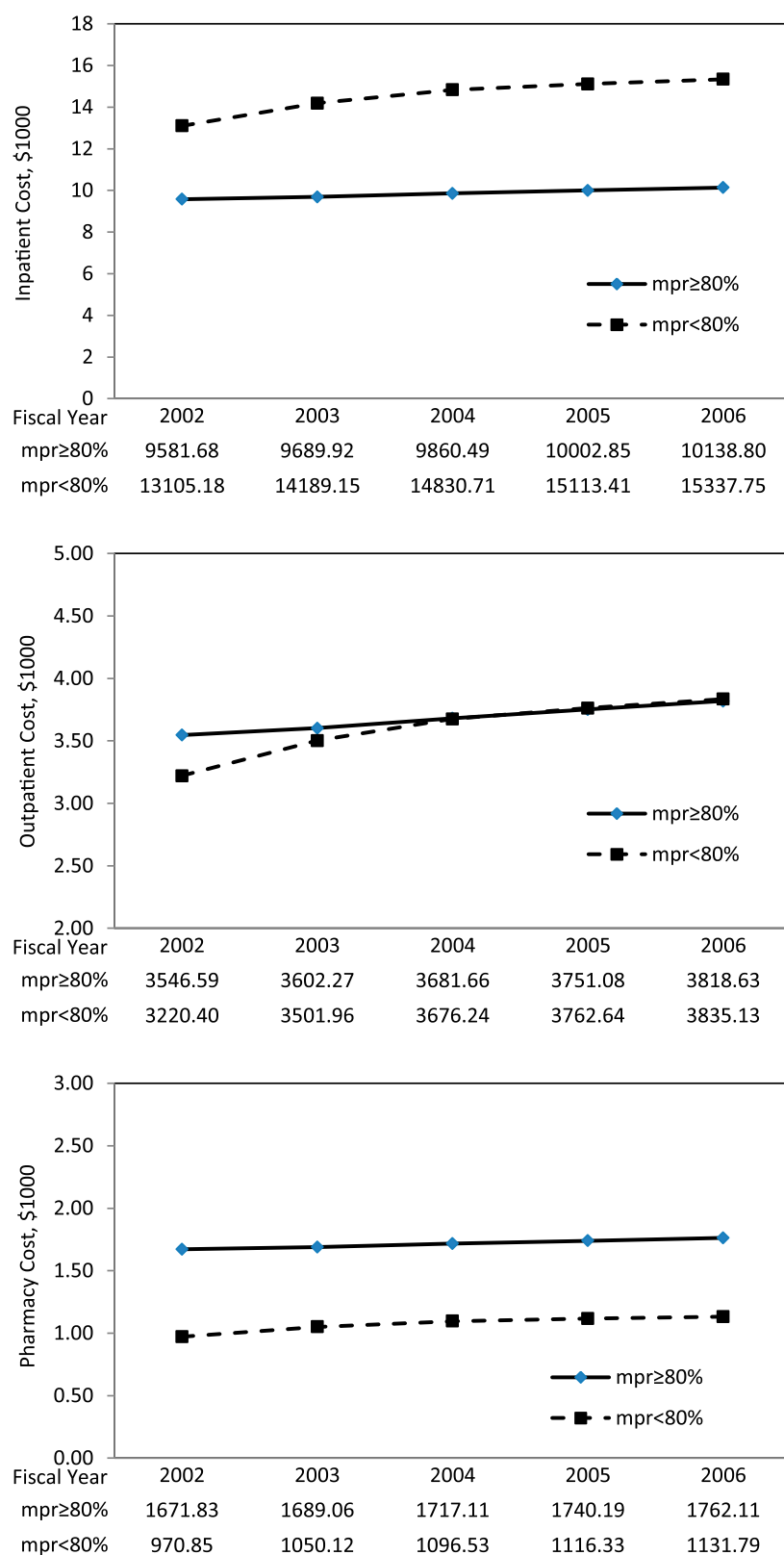
**CONCLUSIONS**—This analysis is one of the first and the largest, to date, to document the longitudinal effects of MNA on different types of healthcare cost. Our analysis demonstrates that the costs of MNA among diabetic patients are quite large and that these costs are mostly driven by inpatient expenditures. The potential cost savings that might be achieved from improving medication adherence are also substantial. These findings are significant both for health services researchers as well as healthcare policy makers.

Although the overall literature on the cost effects of MNA in diabetes is mixed

**Table 1—Demographic and health characteristics of U.S. veterans with type 2 diabetes by medication adherence, 2002–2006**

	All	Adherent (MPR $\geq 80\%$ )	Nonadherent (MPR $< 80\%$ )	P value
n (%)	740,195 (100%)	427,390 (57.7%)	312,805 (42.3%)	
Mean MPR	78.1	93.1	57.7	$<0.0001$
Mean age	65.6	65.4	65.9	$<0.0001$
Male (%)	97.8	98.0	97.5	$<0.0001$
Race (%)				
NHW	69.0	73.0	63.4	$<0.0001$
NHB	12.4	10.2	15.4	
Hispanic	6.1	5.4	7.0	
Missing/other	12.5	11.3	14.2	
Married (%)	65.5	68.2	61.7	$<0.0001$
Service-connected disability $\geq 0.5$	25.6	26.3	24.5	$<0.0001$
Rural (%)	38.7	41.0	35.6	$<0.0001$
Region (%)				
Mid-Atlantic	22.6	23.1	22.3	$<0.0001$
West	15.1	14.6	15.8	$<0.0001$
Northeast	11.2	10.8	11.8	$<0.0001$
South	30.0	29.3	30.9	$<0.0001$
Midwest	20.9	22.2	19.2	$<0.0001$
Comorbidities (%)*				
0	56.5	59.2	52.8	$<0.0001$
1	28.2	27.7	28.9	
2	10.8	9.6	12.4	
3	4.5	3.5	5.9	

\*0, patient had no abuse, cancer, cerebrovascular disease (CBD), congestive heart failure (CHF), cardiovascular disease (CVD), depression, peripheral vascular disease (PVD), or psychosis; 1, patient had one of abuse, cancer, CBD, CHF, CVD, depression, PVD, or psychosis; 2, patient had two of abuse, cancer, CBD, CHF, CVD, depression, PVD, or psychosis; 3, patient had at least three of abuse, cancer, CBD, CHF, CVD, depression, PVD, or psychosis.



**Figure 1**—Trajectory of mean costs from the unadjusted, shared, random intercept log-normal GLMM (in \$1,000 units) for each cost type over time by medication adherence status (veterans with type 2 diabetes 2002–2006). (A high-quality color representation of this figure is available in the online issue.)

(8–10), our findings are consistent with most well-done cross-sectional studies to date that have measured MNA and costs. For example, Balkrishan et al. (10) previously found that each 10% increase in adherence was associated with an 8.6% decrease in total annual healthcare costs. Similarly, Shenolikar et al. (18) reported that a 10% increase in adherence was associated with a 2% reduction in total medical costs and 4% reduction in diabetes-related medical costs.

In order to realize potential health benefits and cost savings, successful interventions are needed that can improve adherence and self-care behaviors among diabetic patients. However, an earlier systematic review of clinical trials designed to improve medication adherence included only two small clinical trials in diabetes (19). In general, these investigators concluded that most successful methods for improving chronic medication adherence were complex, labor intensive, and not predictably effective (19). However, several ongoing trials are currently testing innovative strategies that include individually tailored behavior change interventions, peer health coaching, diabetes self-management website engagement, and technology-assisted case management (20–23). Clearly, further research in this area is needed.

In addition to complex behavioral interventions and technology-based solutions, several healthcare policy changes may contribute to improvements in medication adherence. First, both VHA and non-VHA studies show that decreased cost sharing for those with pharmacy benefits improves medication adherence (24). In the current study, we observed that veterans with high degrees of service connectedness (and thus exempt from copayments) were more likely to be adherent (26.3 vs. 24.5%,  $P < 0.005$ ) (Table 1). This is consistent with an earlier experience in the Rand health insurance experiment (25); although we should note that our study was not designed to specifically examine the effects of copayments on medication adherence. Future studies are needed to determine optimal strategies for modulating copayment levels. Second, expansion of pharmacy benefits to greater numbers of patients should improve both medication adherence and health outcomes. For instance, implementation of Medicare Part D coverage for older Americans was associated with significant improvements in medication use and adherence, with differential

**Table 2—Longitudinal estimates of association of MNA with pharmacy, inpatient, and outpatient costs using generalized linear mixed models**

Effect	Pharmacy cost		Inpatient cost		Outpatient cost	
	Estimates	P value	Estimates	P value	Estimates	P value
Intercept	1,698.60	<0.001	5,744.16	<0.001	5,670.90	<0.001
MNA						
MPR <80%	0.63	<0.001	1.41	<0.001	0.93	<0.001
Fiscal year*	1.03	<0.001	1.03	<0.001	1.03	<0.001
Age	0.99	<0.001	1.00	0.824	0.99	<0.001
Male	0.88	<0.001	1.18	<0.001	0.84	<0.001
Race						
NHB	0.96	<0.001	1.13	<0.001	1.41	<0.001
Hispanic	0.89	<0.001	1.09	<0.001	1.26	<0.001
Others	0.79	<0.001	0.98	<0.001	0.97	<0.001
NHW	Reference		Reference		Reference	
Married	1.06	<0.001	0.77	<0.001	0.79	<0.001
Service-connected disability ≥0.5	1.23	<0.001	1.08	<0.001	1.53	<0.001
Rural	1.00	0.878	1.05	<0.001	0.94	<0.001
West	0.99	<0.001	1.15	<0.001	1.55	<0.001
Northeast	1.04	<0.001	1.10	<0.001	1.10	<0.001
South	1.06	<0.001	0.96	<0.001	1.02	<0.001
Midwest	1.06	<0.001	1.05	<0.001	1.04	<0.001
Comorbidities						
1	1.42	<0.001	1.28	<0.001	1.42	<0.001
2	1.82	<0.001	1.64	<0.001	1.97	<0.001
3	2.26	<0.001	2.22	<0.001	2.89	<0.001
0	Reference		Reference		Reference	

Annual MPR used to define MNA. \*A continuous variable; 2002 as year 1, 2003 as year 2, etc.

reductions in nondrug medical spending for Medicare beneficiaries with limited prior drug coverage (26). Third, medication review visits by clinical pharmacists have been shown to improve appropriate medication prescribing in the elderly, reduce polypharmacy, and reduce adverse drug events in a cost-effective way (27–29). Currently, reimbursement for medication review is either very low or nonexistent by third party payers and thus should be a focus of policy change (30).

Our use of data from the Veterans Affairs Health System is notable for several reasons. First, drawing from the largest integrated health system in the U.S., serving >5.5 million enrollees, our veteran cohort contained comprehensive demographic, clinical, pharmacy, and cost data on a national scale that would have been infeasible to assemble elsewhere (31). Second, although our research group and others have previously demonstrated that racial/ethnic, geographic, and rural/urban

disparities exist in diabetes medication adherence and health outcomes (32,33), there is evidence that quality and equity of care for diabetes is higher within the VHA system (34,35). Third, generous VHA pharmacy benefits may tend to minimize the effects of MNA due to the inability of patients to afford medications. Thus, analyses of VHA data reflect a comprehensive, nationally representative sample where the effects of access, racial/ethnic differences, and medication costs are relatively minimized. These results are relevant for other healthcare systems and payers providing comprehensive healthcare coverage including inpatient, outpatient, and pharmacy benefits.

This analysis is also strengthened by the use of a robust statistical methodology. Analyses of cost data must overcome several statistical problems, including data skewness and heteroscedasticity (11). Longitudinal analyses of cost data must also account for variations in and correlations among cost outlays over time (M.G., Y.A., C.E.D., R.N.A., K. Hunt., L.E.E., unpublished data). In addition, it is desirable to analyze the discrete costs among relevant cost categories (inpatient, outpatient, and pharmacy). Our novel mGLMM technique effectively deals with these issues using a joint modeling with shared random intercept approach. We expect that this type of statistical approach will prove valuable to other research groups analyzing longitudinal cost data in the future.

Nevertheless, our study must be interpreted in light of certain limitations. First, only 2.2% of our sample was female. However, our cohort had >16,000 women. Second, we were unable to control for additional potential cost predictors, such as diabetes self-care behaviors, diabetes disease knowledge, and health

**Table 3—Estimated total potential VHA savings from adherence at various MPR levels in 2012 values\***

Fiscal year	From MPR <1 to 1	From MPR <0.9 to 0.9	From MPR <0.8 to 0.8	From MPR <0.7 to 0.7	From MPR <0.6 to 0.6
2002	\$841,532,100	\$1,024,537,447	\$888,485,131	\$754,127,740	\$628,363,763
2003	\$1,146,874,274	\$1,132,138,936	\$1,001,453,954	\$812,411,421	\$693,528,345
2004	\$1,511,307,098	\$1,365,880,490	\$1,200,610,438	\$922,153,388	\$784,792,619
2005	\$1,124,363,960	\$1,049,113,837	\$932,500,064	\$728,565,709	\$603,561,154
2006	\$1,165,968,163	\$1,095,883,009	\$945,347,155	\$728,484,594	\$597,399,994
Total	\$5,790,045,596	\$5,667,553,720	\$4,968,396,742	\$3,945,742,852	\$3,307,645,875
Mean per year	\$1,158,009,119	\$1,133,510,744	\$993,679,348	\$789,148,570	\$661,529,175
Gains from adherence	\$24,498,375	\$139,831,396	\$204,530,778	\$127,619,395	

\*Source, <http://www.usinflationcalculator.com/>.

beliefs about diabetes, that were not available in our dataset. The collection of such information was not feasible for a cohort so large. Third, our dataset contained a significant proportion of patients who were missing information on race, a consistent problem with other studies in this area. In addition, we did not attempt to separate diabetes-related costs from non-diabetes costs in this analysis because overall cost estimates are of interest for clinicians and policy makers, although this should be the subject of future research. Our analysis is also limited by the absence of cost data from other payers, especially Medicare. Thus, if subjects tended to use non-VHA sources for a large proportion of their healthcare, our estimates of cost may be low. However, our selection criteria, which necessitate multiple VHA visits and prescriptions for diabetes medications, tend to select patients who use the VHA for the majority of their healthcare. Also, because VHA pharmacy copayments tend to be lower than Medicare and private insurance, many veterans fill their prescriptions exclusively at the VHA.

Although MNA has historically received little attention, it has been recognized that improving adherence rates could dramatically impact patient outcomes while reducing overall health care spending (36). Future research in this area is warranted, and it must address additional barriers to medication adherence, including regimen complexity, medication beliefs, and treatment of comorbid depression. However, if successful strategies for improving medication adherence among patients with diabetes can be found, based on our findings, such approaches could fulfill the so-called “triple aim” endorsed by Berwick et al. (37).

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L.E.E. and P.D.M. conceived and designed the study, acquired, analyzed, and interpreted data, and critically revised the manuscript for important intellectual content. M.G. analyzed and interpreted data and drafted and critically revised the manuscript for important

intellectual content. C.E.D., C.P.L., and N.R.A. analyzed and interpreted data and drafted the manuscript. Y.Z. analyzed and interpreted data. All authors approved the final manuscript. L.E.E. and M.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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