

# Medication Adherence and Use of Generic Drug Therapies

Becky A. Briesacher, PhD; Susan E. Andrade, ScD; Hassan Fouayzi, MS;  
and K. Arnold Chan, MD

**Objective:** To assess whether lower copayments charged for generic drugs explain the improved drug adherence associated with use of generics.

**Methods:** We analyzed 2001-2004 healthcare claims data from 45 large employers. Study subjects were age  $\geq 18$  years, had 1 or more of 5 study conditions (hypercholesterolemia, hypertension, hypothyroidism, seizure disorders, type 2 diabetes), and new use of generic-only or brand-only drug therapy for that condition. We measured adherence as the medication possession ratio (MPR), and adequate adherence as MPR  $\geq 80\%$ . Logistic regressions were conducted to assess adequate adherence, adjusting for copayments.

**Results:** We identified 327,629 new users of drug therapy. The proportion starting generic therapies ranged from 9% (hypothyroidism) to 45% (hypertension). After 1 year, 66.2% of individuals with hypothyroidism achieved an MPR  $\geq 80\%$  compared with 53.4% with hypertension, 53.2% with hypercholesterolemia, 52.0% with diabetes, and 42.2% with seizure disorders. Generics were associated with greater adherence than brands in patients with hypercholesterolemia or diabetes ( $P < .05$ ). Lower adherence was seen in patients with hypertension or hypothyroidism ( $P < .05$ ). There was no difference in seizure disorders. The likelihood of achieving an MPR  $\geq 80\%$  with \$0 copayments compared with \$1 to \$9 ranged from an adjusted odds ratio (AOR) of 1.32 for seizure disorders (95% confidence interval [CI] = 1.41, 1.43) to an AOR of 1.45 for hypothyroidism (95% CI = 1.43, 1.48).

**Conclusion:** Generic prescribing was associated with modestly improved adherence in 2 of 5 study conditions. Copayments of \$0 were associated with improved adherence across all conditions.

(*Am J Manag Care. 2009;15(7):450-456*)

For author information and disclosures,  
see end of text.

One of the best documented barriers to medication adherence is high out-of-pocket costs, even among individuals with prescription drug insurance.<sup>1</sup> Numerous studies have found that increased drug copayments are associated with decreased use of prescription drugs, even for highly effective medications used to treat chronic conditions such as diabetes mellitus, hypertension, and hypercholesterolemia.<sup>2-5</sup> As a consequence, it is generally assumed that any government or private health plan policy that reduces copayments will enhance medication adherence.

A current trend in pharmacy benefits is to require relatively small copayments for generic drugs while charging much higher copayments for brand drugs as part of tiered formulary plans. In 2007, employer plans charged, on average, \$11 for generic drugs, \$25 for preferred brand drugs, and \$43 for nonpreferred brand drugs.<sup>6</sup> The wide difference in copayments between generic and brand drugs is especially apparent in the Medicare Part D prescription drug plans, where enrollees pay \$25 to \$60 more for covered brand drugs compared with covered generic drugs.<sup>7</sup> These types of tiered pharmacy benefits steer patients toward generics, which lowers total prescription drug cost but also decreases overall prescription drug use, including for essential therapies.<sup>2</sup> Little is known about why prescription drug use decreases with the introduction of pharmacy benefits that offer incentives for using generics, but the reductions in prescription use are greater than those observed with uniform copayment increases across all brand and generic drugs.<sup>8</sup> This suggests that the relationship between adherence and use of generics may encompass more factors than simply lower copayments. For instance, nonfinancial factors such as chronic disease burden and mood disorders have been found to influence cost-related nonadherence.<sup>1</sup> In addition, research finds consistently that tiered copayments are not associated with lower out-of-pocket costs to individuals but rather with lower costs to the employers and health plans.<sup>8,9</sup> Higher out-of-pocket costs are associated with decreased adherence.

Few previous studies explicitly evaluated the relationship between generic drugs and medication adherence, and those that did reported mixed findings. Furthermore, none to our knowledge explicitly examined the use of generics and medication adherence rates after accounting for the amount of copayments. Two studies of a plan's switch to a generic-

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### Take-Away Points

Analysis of healthcare claims data from 45 large employers showed that generic prescribing was associated with both increases and decreases in medication adherence as well as no effect, depending on the study condition (hypercholesterolemia, hypertension, hypothyroidism, seizure disorders, or type 2 diabetes).

- Copayments of \$0 were a more consistent predictor of increased adherence.
- Cost-related nonadherence and associated negative consequences will likely increase if pharmacy benefits are constructed in such a way as to promote generics without consideration of copayments.

information, diagnoses, procedure codes, and type of provider. For this analysis, we linked the annual files to create a longitudinal panel of continuous observations for each subject.

The study sample included individuals who were age 18 years or older and had a diagnosis of 1 or more of 5 conditions: hyper-

only formulary found significant reductions in the overall use of prescriptions, including decreases in the essential use of angiotensin-converting enzyme inhibitors and statins by patients with diabetes and coronary artery disease, and increases in self-reported financial burden.<sup>10,11</sup> Conversely, a recent study of a tiered pharmacy benefit found adherence was 12.6% higher for patients whose therapy was initiated with generic medications.<sup>12</sup> These studies may not be directly comparable, though, because switching to generics may be a behavior distinct from initiating generics. Nevertheless, none of these analyses accounted for the independent role of copayments, or evaluated whether their findings remained constant across different medical conditions. Our prior research revealed variation in adherence across different medical conditions that might have been influenced by differential access to generic drug formulations.<sup>13</sup> The objectives of this study were to explicitly test the relationship between use of generics and adherence after adjusting for copayments and to see whether the relationship held across different medical conditions.

cholesterolemia, hypertension, hypothyroidism, seizure disorders, and type 2 diabetes. Details of the sample selection are described in a prior study.<sup>13</sup> Briefly these conditions were selected because they are common and treated with chronic drug therapy that is available in generic and brand formulations. (For details about the therapeutic drug classes and diagnostic codes, see the [eAppendix Table, www.ajmc.com](#).) In addition, the study subjects must have initiated new drug therapy for that condition between January 1, 2002, and December 31, 2003. Our analysis used a new user study design to compare the patient groups at the same point in time relative to the initiation of therapy.<sup>15</sup> New drug therapy was defined as a dispensing of a study drug for that condition after at least 1 year of no dispensing of a study drug for that condition. Individuals were excluded if they had missing values or a value of zero or less for the quantity dispensed of the newly initiated study medication ( $n = 11,972$ ), had less than 1 year of follow-up observation after the first dispensing of the study medication ( $n = 588,278$ ), or used both generic and branded therapy during the first year of therapy ( $n = 16,909$ ).

## METHODS

### Study Population and Data Sources

The study data were drawn from the 2001-2004 Market Scan Research databases (MEDSTAT, Ann Arbor, MI). These are secondary data sets of employer-sponsored medical care claims, prescription drug claims, and healthcare encounter data from approximately 45 large US employers and public organizations. The data are based on a nationwide sample but are limited in generalizability for certain groups, particularly for employees and their dependents of small and medium firms and the unemployed. Each year of the data set contains medical care information on 3 million to 6 million individuals, and scientific studies based on this data source have been reported in more than 40 peer-reviewed articles.<sup>14</sup> The encounter files contain age, sex, geographic residence, and eligibility information. The prescription claims file includes the national drug codes, date of purchase, quantity dispensed, days supply, and expenditure information for each dispensing. The medical claims file contains payment

### Medication Adherence

We used the medication possession ratio (MPR) to measure prescription drug adherence.<sup>16</sup> The MPR is the days supply of medication dispensed during the follow-up year divided by the number of days in the year. A recent review of adherence measures shows MPR is a reliable measure of adherence.<sup>17</sup> Our calculation included dispensings for the initial study drug therapy as well as for all other study drug therapies for that condition. Overlaps in the dispensing days of different generic drug therapies were eliminated, under the assumption that leftover supplies from earlier refills were discarded to begin the newer medication (eg, a change in therapy). Overlaps in the dispensing days of the same generic drug therapies were summed, under the assumption that earlier refills still were taken by the patient as part of the same regimen (eg, an early refill). The value of the days supply was truncated if the supply extended beyond the time period of observation. In addition, MPR values  $>100\%$  were truncated to a value of 100%. Overadherence is difficult to interpret as

■ **Table 1.** Characteristics of Study Population (n = 327,629)

Characteristic	Value
<b>Age, mean (SD), y</b>	56.6 (12.3)
<b>Comorbidity score, mean (SD)</b>	0.56 (0.60)
<b>Sex, %</b>	
Male	46.8
Female	53.2
<b>Geographic residence, %</b>	
Northeast	10.6
North Central	31.2
South	40.4
West	17.7
<b>Type of health plan, %</b>	
Comprehensive	31.1
Preferred provider organization	38.3
Point-of-service	20.9
Health maintenance organization	8.7
Exclusive provider organization	1.0
<b>Selected chronic conditions,<sup>a</sup> %</b>	
Hypercholesterolemia	47.8
Hypertension	38.3
Type 2 diabetes	12.6
Hypothyroidism	9.3
Seizure disorders	0.6

<sup>a</sup>Not mutually exclusive categories.

we were unable to differentiate between inappropriate behaviors (eg, overuse, early refills) and appropriate behaviors (eg, changes in drug regimens, combination therapies, multiple dispensings to achieve a specific dose). Adequate adherence was defined as MPR  $\geq 80\%$ , although sensitivity analyses were conducted at MPR  $\geq 60\%$ .

### Other Measures

Generic formulations of the study drugs were identified using a generic product indicator variable for each drug in each year of the database to flag generic preparations. The study copayment was identified as the modal value of all copayments provided for any study medications dispensed during the year, as used previously.<sup>18,19</sup> The mean copayment (standard deviation) for each condition was as follows: seizure disorders \$15.10 (\$13.50 SD); hypothyroidism \$9.90 (\$7.70 SD); type 2 diabetes \$13.50 (\$12.90 SD); hypercholesterolemia \$18.80 (\$15.50 SD); and hypertension \$13.10 (\$12.50 SD). Based on the modal copayment distribution, individuals were categorized as having copayment levels of

\$0, low (\$1-\$9), medium (\$10-\$29), and high (\$30+). In addition, we evaluated the effect of prescription drug adherence with the following covariates: age, sex, plan type, geographic residence, and comorbidity level. Comorbidity level was generated using the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) system (DxCG, Boston, MA).<sup>20,21</sup> The DCG/HCC risk adjuster creates a single score for each individual based on the diagnosis fields of claims records. Each individual was assigned an index date based on the first dispensing of the newly initiated drug therapy. Data from the year before the index date were used to calculate the comorbidity risk score. Data from the year after the index date were used to measure adherence and copayment level.

### Statistical Analysis

Bivariate statistics were used to assess the unadjusted means and frequency distributions of the study variables. Logistic regression models were used to estimate the associations (adjusted odds ratios [AORs] and 95% confidence intervals [CIs]) between adequate adherence and generic medication use for each disease state. Multicollinearity was assessed using the variance inflation factor (VIF) and the general rule of thumb that a VIF value of more than 10 indicates severe multicollinearity. None of the VIF values for our copayment variables or generic variables in any of the models exceeded the value of 4, and most were less than 2.5.

## RESULTS

We identified 327,629 individuals with 1 of 5 chronic medical conditions and newly initiated drug therapy for that condition (Table 1). The average age of the subjects was 57 years, 53% were female, and the mean comorbidity score was  $0.56 \pm 0.60$ . Approximately 40% of the subjects lived in the southern part of the United States, followed by 31% in the north-central region. Preferred provider organizations were the most common type of health coverage (38%), followed by comprehensive plans (31%) and point-of-service plans (21%). About 48% of the individuals had hypercholesterolemia, 38% had hypertension, 13% had type 2 diabetes, 9% had hypothyroidism, and 1% had seizure disorders.

Table 2 shows a distribution of individuals by use of generics and copayment levels for study medication. The proportion who initiated therapy with generic drugs was 6% for hypercholesterolemia, 9% for hypothyroidism, 27% for seizure disorders, 37% for type 2 diabetes, and 45% for hypertension.

■ **Table 2.** Distribution of New Drug Users by Generic/Brand Use and Drug Copayment

Study Condition	Percentage of Users by Copayment Level (n)				Total No.
	\$0	\$1-\$9	\$10-\$29	\$30+	
<b>Seizure disorders</b>					
Generic users	9 (46)	61 (296)	24 (115)	6 (29)	486
Brand users	8 (110)	15 (199)	37 (495)	40 (538)	1342
<b>Hypothyroidism</b>					
Generic users	7 (207)	74 (2067)	16 (458)	2 (63)	2795
Brand users	10 (2879)	36 (9972)	42 (11,723)	12 (3201)	27,775
<b>Type 2 diabetes</b>					
Generic users	11 (1699)	58 (8809)	25 (3714)	6 (935)	15,157
Brand users	13 (3344)	19 (4941)	24 (6370)	44 (11,434)	26,089
<b>Hypercholesterolemia</b>					
Generic users	6 (633)	71 (6960)	17 (1670)	6 (555)	9818
Brand users	12 (17,449)	14 (20,376)	22 (31,695)	53 (77,241)	146,761
<b>Hypertension</b>					
Generic users	10 (5752)	65 (36,705)	21 (11,897)	4 (2044)	56,398
Brand users	10 (7199)	17 (11,709)	24 (16,322)	49 (33,769)	68,999

In general, most generic users had copayments within the range of \$1 to \$9, comprising 58% to 74% of these populations in each disease group. However, brand users had a wider range of copayments, which varied by disease. For instance, copayments of \$30 or more were paid by 53% of brand users who had hypercholesterolemia, compared with 12% of brand users who had hypothyroidism. Interestingly, brand users and generic users were equally likely to pay \$0 copayments, except in 1 case: 12% of brand users who had hypercholesterolemia paid \$0 copayments compared with 6% of generic users who had hypercholesterolemia.

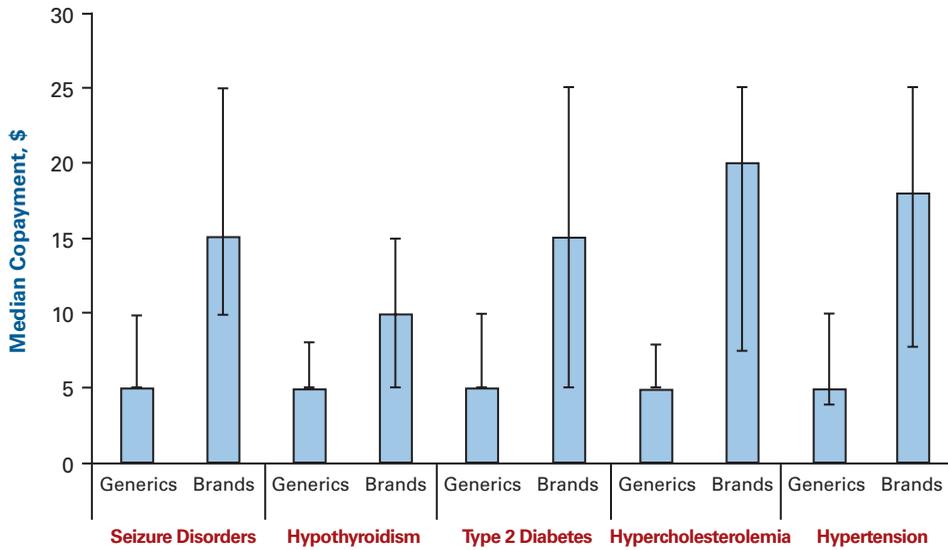
**Figure 1** shows the distribution of new users by the median copayment paid for the study drug therapy. New users who initiated therapy with generic drugs paid out-of-pocket, on average, \$5 for their prescription, while new users who initiated therapy with brand drugs paid out-of-pocket, on average, \$10 to \$20 for their prescription. This figure also shows that the variation around generic copayments is modest, with the interquartile range within \$4 to \$10 for all conditions; the variation around brand copayments is larger, with the interquartile range spanning \$5 to \$25.

**Figure 2** shows the overall proportion of individuals achieving adequate adherence. Individuals with seizure disorders had the lowest rates of adherence: 43% and 39% of brand users and generic users, respectively, achieved MPRs  $\geq 80\%$ . Individuals with hypothyroidism achieved the highest MPRs, approximately two-thirds of the population, regard-

less of brand or generic use. Use of generics was significantly associated with higher adherence only for individuals being treated for hypercholesterolemia (62% vs 53%;  $P < .0001$ ). Conversely, use of generics was significantly associated with lower adherence when the treatment was for hypertension (47% vs 59%;  $P < .0001$ ). There was no difference in adherence between brand and generic users for those with diabetes or seizure disorders.

**Table 3** shows the multiple regression results. In model 3 with the full model specification, use of generics was associated with significantly better adherence relative to use of brands in individuals with 2 conditions (hypercholesterolemia AOR = 1.52, 95% CI = 1.44, 1.60; diabetes AOR = 1.06, 95% CI = 1.01, 1.12), significantly poorer adherence in individuals with 2 conditions (hypertension AOR = 0.75, 95% CI = 0.73, 0.77; hypothyroidism AOR = 0.86, 95% CI = 0.78, 0.94), and no difference in individuals with seizure disorders, after controlling for copayment levels and other covariates. In comparison, \$0 copayments were associated with adequate adherence across all 5 conditions. For instance, relative to \$0 copayments, the likelihood of achieving adequate adherence decreased for all conditions with \$1 to \$9 copayments, ranging from an AOR of 0.47 for seizure disorders (95% CI = 0.32, 0.68) to an AOR of 0.83 for hypothyroidism (95% CI = 0.76, 0.91), controlling for generic use and other covariates. Exceptions to the higher adherence with the \$0 copayment occurred only at the highest copayment levels (\$30+) for individuals with hypothyroidism

■ **Figure 1.** Distribution of Copayments for Study Drugs



Black bars show interquartile range.

or hypertension. The sensitivity analysis with adequate adherence set at MPR  $\geq 60\%$  showed similar results.

## DISCUSSION

In this study of more than 300,000 privately insured adults age 18 years or older, we found the use of generic drug therapy was inconsistently associated with improved adherence, and the effects were generally small. In 2 of 5 chronic conditions, patients were more likely to achieve MPR levels of 80% or higher if taking generics rather than brands: only patients with hypercholesterolemia or diabetes had improved adherence if taking generic drugs rather than brand drugs, after controlling for differences in copayments. Conversely, patients with hypertension or hypothyroidism had poorer adherence if taking generic rather than brand drug therapy, and patients with seizure disorders experienced no difference in adherence. A \$0 copayment was the strongest and most consistent predictor of adequate adherence in the study conditions, regardless of the use of generics or brands.

What could account for the inconsistency we found in levels of adherence with generic drug therapy? This study cannot answer this question; however, at least 1 other study found that some patients rate generics as less important than brand drugs and that the importance rating predicts adherence.<sup>22</sup> It also is possible that some issues specific to certain medications (eg, the bioequivalence of generic and brand formulations of levothyroxine) may have influenced these results.<sup>23</sup> Also, some conditions have had generic drug therapies available for more years than others and also have more

generic choices from which to select. The number of unique generic and brand names for our study conditions were 76 brands and 45 generics for hypertension; 16 brands and 9 generics for type 2 diabetes; 8 brands and 6 generics for seizure disorders; 8 brands and 1 generic for seizure disorders; and 4 brands and 2 generics for hypothyroidism. The relationship between these differences and our findings is not clear. We investigated the possibility that the magnitude of difference between generic and brand copayments influenced adherence, but could discern no clear pattern. For instance, the copayment differential between generics and brands was greatest for hypercholesterolemia (\$19.50 brand vs \$7.10 generic) and hypertension (\$18.50 vs \$6.60 generic), yet generic use resulted in better adherence in hypercholesterolemia and poorer adherence in hypertension. Our sensitivity analysis lowering the adequate adherence level to  $\geq 60\%$  showed nearly identical results, and an ad hoc analysis excluding mail order prescriptions also revealed no consistent patterns.

Our study offers several unique contributions that distinguish it from other studies. First, our study population was incidence users, whereas nearly all other studies of cost-sharing and adherence examined prevalence users.<sup>2,3,5</sup> It has been our experience that incidence users are different from prevalence users; most notably, their adherence levels are generally lower than those of prevalence users (at least 10 percentage points lower). Furthermore, our measure of adherence included a broad range of drug classes and our sample selection criteria had few exclusions, whereas most other studies focused on individual drug classes and specific patient populations. In our review of the literature, we could find no other comparable studies for external validation. Thus, the strength of our study is in the uniform comparison of the relative effects of generic use on adherence across 5 different patient populations in the first year of therapy.

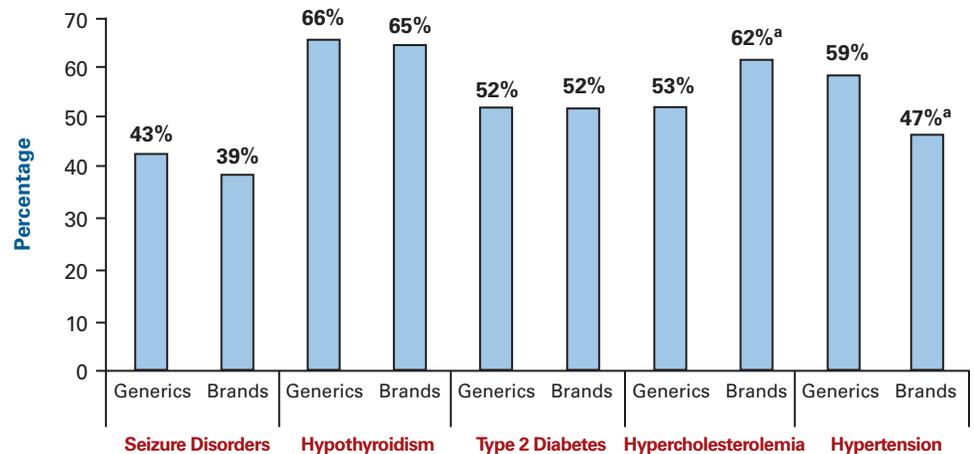
This study had several limitations. The selection of chronic medical conditions was a somewhat arbitrary process that was limited to conditions treated most often with prescribed drug therapies taken on a regular and daily basis. For instance,

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arthritis was not selected because of the common use of over-the-counter medications and medications on an as-needed basis. There also were overlaps in the samples because we did not limit the individuals to a primary diagnosis. The largest overlap was 17%, and it occurred between the samples for hypertension and hypercholesterolemia. This study used the MPR and pharmacy claims records to measure adherence. Thus, our analysis assessed rates of medication acquisition

rather than medication exposure. However, research has demonstrated predictive validity for measuring the cumulative exposure of medications with acquisition data.<sup>24</sup> Indeed, our measure of adherence depends on the accuracy of the days

**Figure 2.** Proportion of Individuals With a Medication Possession Ratio of  $\geq 80\%$



<sup>a</sup> $P < .05$ .

supply information, although we have no evidence of measurement bias related to the drug class or specific disease state being treated.<sup>25</sup> The MPR provides only 1 measure of adherence, and other types of adherence measures may provide dif-

**Table 3.** Logistic Regressions Evaluating Adequate Adherence by Use of Generics

Predictors of Adequate Adherence	Adjusted Odds Ratio (95% Confidence Interval)				
	Seizure Disorders (n = 1828)	Hypothyroidism (n = 30,570)	Type 2 Diabetes (n = 41,246)	Hypercholesterolemia (n = 156,579)	Hypertension (n = 125,397)
<b>Model 1: use of generics, unadjusted</b>					
Generics (reference: brands)	0.84 (0.68, 1.03)	0.94 (0.86, 1.01)	1.02 (0.98, 1.06)	1.47 <sup>a</sup> (1.41, 1.53)	0.62 <sup>a</sup> (0.60, 0.63)
<b>Model 2: use of generics adjusted for only copayments</b>					
Generics (reference: brands)	0.95 (0.75, 1.21)	0.91 <sup>a</sup> (0.84, 0.99)	1.02 (0.98, 1.07)	1.53 <sup>a</sup> (1.46, 1.60)	0.69 <sup>a</sup> (0.68, 0.71)
<b>Copayment levels</b>					
\$0 (reference)					
\$1-\$9	0.49 <sup>a</sup>	0.80 <sup>a</sup>	0.75 <sup>a</sup>	0.66 <sup>a</sup>	0.68 <sup>a</sup>
\$10-\$29	0.63 <sup>a</sup>	0.71 <sup>a</sup>	0.72 <sup>a</sup>	0.60 <sup>a</sup>	0.79 <sup>a</sup>
$\geq$ \$30	0.70	1.30 <sup>a</sup>	0.77 <sup>a</sup>	0.82 <sup>a</sup>	1.00
<b>Model 3: use of generics adjusted for copayments and other characteristics<sup>b</sup></b>					
Generics (reference: brands)	0.88 (0.69, 1.14)	0.86 <sup>a</sup> (0.78, 0.94)	1.06 <sup>a</sup> (1.01, 1.12)	1.52 <sup>a</sup> (1.44, 1.60)	0.75 <sup>a</sup> (0.73, 0.77)
<b>Copayment levels</b>					
\$0 (reference)					
\$1-\$9	0.47 <sup>a</sup>	0.83 <sup>a</sup>	0.73 <sup>a</sup>	0.68 <sup>a</sup>	0.72 <sup>a</sup>
\$10-\$29	0.61 <sup>a</sup>	0.84 <sup>a</sup>	0.80 <sup>a</sup>	0.66 <sup>a</sup>	1.02
$\geq$ \$30	0.75	1.57 <sup>a</sup>	0.92	0.93 <sup>a</sup>	1.32 <sup>a</sup>

<sup>a</sup>Significant at  $P < .05$ .

<sup>b</sup>Adjustments were age, sex, plan type, geographic residence, and normalized comorbidity risk score.

ferent results, although we have no evidence to suspect that generic use is sensitive to the particular adherence metric.<sup>26</sup> In addition, we have no information about whether the drug therapy was prescribed for primary or secondary prevention for certain conditions. Lastly, we excluded individuals taking both generics and brands. These individuals may have affected the results for certain patient groups more than others, although this criterion affected only about 10% of the sample.

Despite these limitations, this study offers one of the first uniform assessments of the impact of generic use on adherence across multiple conditions and after controlling for copayments. We conclude that a \$0 or very low copayment will more consistently improve adherence than use of generics, and the improvement will be larger, at least for the 5 chronic medical conditions studied here. This finding is not surprising given that lowering the copayment is a more direct way to lower a patient's out-of-pocket burden than prescribing generics. However, this finding also should serve as an important reminder that adherence may be at risk when copayments increase, even if generics are available. The clinical implication of these findings is to discourage prescribing practices and formulary designs that promote generic drug therapies as an across-the-board solution to cost-related nonadherence: cost-related nonadherence and associated negative consequences will likely increase if pharmacy benefits are constructed in such a way as to promote generics without consideration of copayments.

**Author Affiliations:** From the Division of Geriatric Medicine (BAB, HF), Department of Medicine (SEA), University of Massachusetts, Worcester; Meyers Primary Care Institute (BAB, SEA, HF), Worcester, MA; the Department of Epidemiology (KAC), Harvard University, Boston, MA; and Brigham and Women's Hospital (KAC), Boston, MA.

**Funding Source:** This study was funded by an unrestricted research grant from Novartis Pharmaceuticals Corporation, East Hanover, NJ.

**Author Disclosure:** Drs Briesacher and Andrade report receiving and having grants pending from Novartis Pharmaceuticals. The other authors (HF, KAC) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

**Authorship Information:** Concept and design (BAB, SEA, KAC); acquisition of data (BAB, KAC); analysis and interpretation of data (BAB, SEA, HF, KAC); drafting of the manuscript (BAB, HF); critical revision of the manuscript for important intellectual content (BAB, SEA, KAC); statistical analysis (BAB, HF); and obtaining funding (BAB).

**Address correspondence to:** Becky A. Briesacher, PhD, Division of Geriatric Medicine, University of Massachusetts, 377 Plantation St, Biotech Four, Ste 315, Worcester, MA 01605. E-mail: becky.briesacher@umassmed.edu.

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