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original contributions

Medication Adherence Among Adults With Comorbid Chronic Conditions Initiating Oral Anticancer Agent Therapy for Multiple Myeloma

Justin Gatwood, PhD, MPH[1]; Ankur Dashputre, PhD[1]; Abhijeet Rajpurohit, MS[2]; Katie Gatwood, PharmD[3]; Emily Mackler, PharmD[4]; Leah Wallace, BS[1]; Karen Farris, PhD[4]; Amna Rizvi-Toner, PharmD, MPH[4]; and Joel Farley, PhD[2]

QUESTION ASKED: To what extent does initiating an oral anticancer agent (OAA) affect adherence to medications being taken for pre-existing chronic diseases among adults with multiple myeloma (MM) and multiple chronic conditions?

SUMMARY ANSWER: Adherence to medications for select, high-prevalence chronic conditions generally declined in the year after OAA initiation. Moreover, changes were particularly prominent among commercially insured adults on antihypertensive therapy who were nonadherent to their OAA.

WHAT WE DID: This was a retrospective cohort study using medical claims from commercial (MarketScan) and Medicare data sets from 2013 to 2018. Eligible patients included adults diagnosed with and being treated for MM who were initiating an OAA for the first time. In addition, patients must have had at least two pre-existing chronic conditions for which they were taking medication, records for which must have been available for the both the year before and after OAA initiation. Analyses focused on OAA adherence, chronic disease medication adherence, and changes in chronic disease medication use in the year after OAA initiation.

WHAT WE FOUND: Adherence to OAA treatment among adults with MM was suboptimal in the first year of therapy, averaging 58.3% (standard deviation: 24.5) and 65.1% (standard deviation: 27.01) for commercially insured and Medicare patients, respectively. After controlling for patient characteristics, significant declines in antihypertensive medication adherence were observed among adults nonadherent to their OAA compared with those adherent to their OAA in the first year of treatment (difference-in-differences: –5.2% [commercial] and –2.5% [Medicare], $P < .05$). Similarly, for Medicare patients, those nonadherent to their OAA were observed to have a significant decline in adherence to statins compared with adults adherent to their OAA in the first year of therapy (unadjusted difference-in-differences: –3.6%, $P < .05$).

BIAS, CONFOUNDING FACTORS, REAL-LIFE IMPLICATIONS: Assessing medication use through medical claims relies on calculating indirect metrics of adherence, which only reflects whether medication could have been taken and not actual consumption. Consequently, the reported adherence levels may not reflect actual use, for either the OAA or chronic disease medications. In addition, factors included in the multivariate analyses were limited to the patient and clinical characteristics available in the referenced data sets; however, it is likely that other characteristics or events not accounted for in these data might have affected adherence (eg, side effects and access). The likelihood of patients having multiple chronic conditions at the time of MM treatment initiation is high, particularly among older adults. Therefore, clinicians must consider the entire regimen when counseling patients on the importance of medication adherence in achieving stated treatment goals. In doing so, providers signal to their patients with MM a commitment to improving the odds of positive cancer-related and chronic disease–related health outcomes.

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abstract

PURPOSE Increased use of oral anticancer agents (OAAs) has empowered adults with multiple myeloma (MM) to manage their oncolytic therapy, but such a shift may result in issues with medication use, particularly among patients being concurrently treated for pre-existing, multiple chronic conditions.

METHODS This retrospective cohort study used 2013-2018 commercial and Medicare claims data to assess medication use in adults with MM. To be included, adults (18 years and older) must have been diagnosed with and had 2+ claims for an OAA, had continuous enrollment for 12 months before and after OAA initiation, and have been previously diagnosed with and had prescription fills for 2+ select chronic conditions. The proportion of days covered metric assessed medication adherence and was compared for 12 months before and after the OAA initiation by Wilcoxon signed-rank tests, McNemar's tests, and difference-in-differences models.

RESULTS The mean OAA adherence in the first year of therapy was 58.3% (standard deviation: 24.5) and 65.1% (standard deviation: 27.01) for commercial and Medicare patients, respectively. Adherence and the proportion adherent (proportion of days covered $\geq$ 80%) to comorbid therapies generally declined in the first year after OAA initiation. Changes in medication use were particularly noticeable among those on antihypertensive therapy: adjusted analyses uncovered a 2.5% (Medicare) and 5.2% (commercial) difference in adherence to these medications between those initially adherent and nonadherent to OAA therapy (both $P < .05$).

CONCLUSION Initiating OAA therapy in adults with MM may complicate an already complex treatment regimen, resulting in poor overall medication adherence in patients with multiple comorbid conditions.

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INTRODUCTION

Since 2000, the incidence of multiple myeloma (MM) has increased in the overall US population, with notably larger increases observed among certain subgroups, such as adults age 40-49 years, non-Hispanic White men, and non-Hispanic Black men.[1-3] Fortunately, over the same period, 5-year survival rates demonstrated significant improvement, increasing from 35% to 53% as of 2017.[3] Much of this success in improving survival can be attributed to the availability of new therapies, with more than a dozen having been approved in the past decade. Importantly, many of these therapies are available in oral formulations, empowering patients to self-manage their MM. However, this shift toward self-management also increases the risk for medication nonadherence, particularly given the often-complex regimen required to manage MM effectively.[4-6]

Adherence to oral anticancer agents (OAAs) among patients with MM varies considerably, with estimates ranging from 58% to 89.5%, depending on the metric used and medication assessed.[7-11] Factors that have been shown to influence adherence to OAA among patients with MM include, but are not limited to, regimen complexity, medication toxicity, cognitive impairment, poor patient-provider communication, restrictive distribution of products by the manufacturer, the burdensome Risk Evaluation and Mitigation Strategy process, and cost.[4,6,12-14] One factor that has particular relevance to the risk of nonadherence in patients with MM is medication complexity associated with polypharmacy (the use of multiple concurrent medications) to manage comorbid chronic conditions. Considering the relatively late onset of MM, the likelihood of needing to manage OAA simultaneously and other treatments is high.[16] Previous evidence suggests

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that the pill burden associated with using multiple medications to manage multiple chronic conditions increases the risk for medication nonadherence in MM.[15]

The objective of this research was to examine initial adherence to OAAs in adult patients with MM and the impact of such initiation on adherence to medications for existing comorbid chronic conditions. The results of this study will help to identify patient characteristics that providers may refer when prescribing OAA therapy to address the importance of total regimen adherence during encounters. This information may help providers as they assist patients in navigating treatment for a range of conditions and for which a number of influencers may affect ongoing adherence.

METHODS

Study Design

This study used a retrospective cohort study design to examine OAA adherence and adherence to prescription medications used for multiple chronic conditions among adult patients diagnosed with MM. We used a 1-year preobservation washout period to identify new OAA initiation and to identify patient characteristics predictive of OAA adherence. Outcomes were observed during a 1-year postobservation period from the index date of OAA initiation.

Data

Two secondary claims data sources were used to capture a younger commercially insured and older Medicare population. Commercially insured patients were captured using IBM MarketScan Commercial Claims and Encounters (CCAE) data. These data represent a broad population of beneficiaries with both private and employer-sponsored health insurance. Medicare beneficiaries were captured using a 20% random sample of patients with Parts A (inpatient), B (outpatient), and D (prescription) coverage. These data sources are deidentified, and this research was deemed exempt from full human subjects review by each institution's Institutional Review Board.

Population Selection

Patients with MM were included if they had International Classification of Disease, ninth and 10th revision codes 203.0x and C90.0x, respectively. Given the emphasis on OAA adherence, we limited the sample to patients filling two or more OAA prescriptions within 1 year of the initial cancer diagnosis date. OAA medications for MM included thalidomide, lenalidomide, and pomalidomide. To ensure complete measurement of medication adherence, we required patients to be continuously enrolled in outpatient, inpatient, and prescription drug benefits throughout the 1-year pre- and postperiod in both data sources. The Medicare population was further restricted to patients enrolled through age (65 years and older) or disability qualifications by excluding patients eligible because of End-Stage Renal Disease. A small number of patients were excluded because of the presence of two or more concurrent hematologic cancers (eg, chronic myeloid and chronic lymphocytic leukemia). Finally, given the emphasis on comorbid medication adherence, patients were only included if they filled two or more prescriptions for two or more comorbid conditions during both the pre- and postobservation periods. To facilitate adherence measurement for therapeutic classes, we required at least one of the two comorbid conditions to be type-two diabetes mellitus, hypertension, or hyperlipidemia. Patients were excluded if they had an existing diagnosis for HIV or were observed to have undergone stem-cell transplant within the first year of OAA initiation, which was instituted because of the interruption in oral therapy before and after this procedure. The final sample represents patients with MM using OAA with multiple chronic conditions managed by prescription medication both before and after an incident diagnosis of hematologic cancer.

Patient Characteristics

We constructed a number of demographic variables, including age, sex, geographic region (Northeast, Midwest [North Central in CCAE], South, and West), and residence within an urban metropolitan statistical area. The Elixhauser Index was used to identify comorbid health conditions, and this metric is a count of 38 pre-existing conditions that are often controlled for to account for their influence on resource utilization and, potentially, health outcomes.[17] A count of unique therapeutic medication classes used during the 1-year preperiod captured medication burden. Health insurance generosity was captured in MarketScan if beneficiaries were enrolled in either preferred or exclusive provider organizations, with other beneficiaries labeled having less generous coverage. In Medicare, patients enrolled with a form of low-income subsidy (eg, dual Medicaid coverage or enrollment in a subsidized low-income or qualified Medicare benefit) were compared with patients with no low-income subsidy. Although not available in MarketScan, we categorized race/ethnicity for Medicare patients as White/non-Hispanic, Black/non-Hispanic, Hispanic, or Others/unknown. Using the index oncolytic, patients were categorized as filling medications through mail order, retail, or other/missing pharmacies. Finally, the index fill was used to calculate quartiles of oral oncolytic co-payment as a measure of prescription insurance generosity. Quartiles were calculated separately for the MarketScan and Medicare samples, given substantial differences in co-payment amounts between cohorts.

Medication Adherence

Medication adherence was measured using the proportion of days covered (PDC). The PDC calculates the proportion of days in which a patient has medication on hand throughout the observation window using prescription fill dates and day supply to calculate periods of medication coverage.[18] For OAA adherence, we observed the PDC from

the date of OAA initiation (the study index date). For comorbid medications, the PDC observation window encompassed comorbid prescription refills in the year before and after the OAA index date. Comorbid medication adherence was captured for oral antidiabetic medications, which included drug classes coded in the Centers for Medicare and Medicaid Service Star Ratings program (biguanides, sulfonylureas, thiazolidinediones, dipeptyl peptidase inhibitors, meglitinides, glucagon-like peptide-1 agonists, and sodium-glucose cotransporter-2 inhibitors), HMG-CoA reductase inhibitors (statins) for hyperlipidemia, and antihypertensive agents, which included angiotensin receptor blockers II, angiotensin-converting enzyme inhibitors, thiazide, potassium-sparing, and loop diuretics, beta-blockers, alpha-blockers, calcium channel blockers, central agonists, peripheral adrenergic blockers, and vasodilators.[19] We followed Centers for Medicare and Medicaid Service Medicare Star Ratings technical specification guidance to adjust the PDC for periods in which a person was hospitalized.[20] The PDC was dichotomized at a commonly accepted clinical threshold of adherence for patients with PDC $\geq$ 80%. For OAA adherence, we recognized that 80% adherence might not be clinically acceptable for achieving therapeutic goals and varied this level in sensitivity analyses to examine 85% and 90% PDC thresholds.[10]

Analysis

Patient characteristics were described using mean (plus standard deviation [SD]) for continuous variables and counts (plus percentages) for categorical variables. Changes in adherence to comorbid therapies from baseline to the follow-up period were assessed using Wilcoxon signed-rank tests. An unadjusted difference-in-differences (DiD) model was used to assess whether OAA adherence affected change in adherence for comorbid therapies from baseline to follow-up. An unadjusted DiD model assessed comorbid therapy adherence changes across the base case (PDC 80%) and sensitivity (PDC 85% and PDC 90%) adherence thresholds for OAAs to test for model robustness. In addition, univariate logistic regression was used to assess the association between baseline comorbid therapy nonadherence and OAA nonadherence; a similar model tested the association between OAA nonadherence and follow-up comorbid therapy nonadherence among those adherent to comorbid therapy in the baseline period. Nonadherence was defined as PDC $<$ 80% for comorbid therapy (both in baseline and follow-up) and as PDC $<$ 80% (base case) and PDC $<$ 85% and PDC $<$ 90% (sensitivity) for OAAs. All logistic regression models reported odds ratios and 95% CIs. McNemar's tests assessed the change in the proportion of patients adherent/nonadherent to comorbid therapy from baseline to follow-up. Pearson correlation analysis assessed the relationship between OAA adherence and adherence to comorbid therapies in the follow-up period. A two-sided *P* value of $<$ .05 was considered statistically significant.

RESULTS

Table 1 shows attrition associated with applying our inclusion and exclusion criteria. Beginning with a sample of 32,848 CCAE and 34,241 Medicare beneficiaries, the largest reductions in the sample resulted from limiting the sample to patients filling medications for two or more comorbid conditions and the application of continuous enrollment, both of which are needed to capture OAA adherence accurately. After applying these restrictions, our sample contained 6,656 CCAE and 8,590 Medicare patients, respectively. Further limiting the sample to patients with multiple chronic conditions using medications to manage these conditions before and after OAA initiation, our sample was reduced to 732 CCAE and 2,040 Medicare patients. The final sample, after limiting to patients age 18 years and older without a history of HIV or evidence of stem-cell transplant, resulted in a final sample of 585 CCAE and 1,865 Medicare patients using an OAA to manage MM with multiple chronic conditions managed by prescription medication.

In terms of OAA adherence in the first year of therapy, the mean PDC for commercial patients was 58.3% (SD: 24.5) and 65.1% (SD: 27.01) for Medicare patients; median values were 57.0% (interquartile range: 38-79) for commercially insured adults and 72.0% (interquartile range: 43-90) for Medicare patients. Table 2 compares patients who are adherent or nonadherent to OAA medication as defined by a PDC of 80% or higher. Notably, 141 patients of the 585 patients (24.1%) in the CCAE cohort and 780 of the 1865 patients (41.8%) in the Medicare sample were considered adherent to OAA medication. Using an alternative PDC threshold of 85% to be considered adherent, these proportions drop to 19.8% and 34.5% for commercial or Medicare patients, respectively; using a 90% PDC threshold to be considered adherent, the proportions are 15.4% and 26.1% for commercial and Medicare, respectively. No statistical differences were noted in either the CCAE or Medicare sample in the proportion of patients labeled adherent on the basis of age, sex, urban versus rural residence, or region in which a patient who resides in the US Nonadherent OAA patients in the Medicare sample tended to have higher rates of comorbid hypertension (95.5% *v*92.9%, $P = .019$), diabetes (44.5% *v*35.6%, $P < .001$), and hyperlipidemia (72.8% *v*68.3%, $P = .036$) than adherent OAA patients. Patients in both the CCAE and Medicare sample who were nonadherent to OAA medications also tended to have higher disease and treatment burden as defined by the sum of Elixhauser conditions present and therapeutic drug categories used during the 1-year pre-OAA initiation period. To illustrate, in the CCAE sample, the number of Elixhauser conditions among nonadherent OAA users was 7.0 (SD = 6.8) compared with 6.3 (SD = 5.9) conditions in adherent OAA users ($P = .012$). In the Medicare sample, counts of unique therapeutic classes of medication used averaged

TABLE 1. Population Inclusion and Exclusion Criteria

Step	Criteria	CCAE (No.)	Medicare 20% (No.)
1	MM diagnosis		
	ICD-9 203.0x or ICD-10 C90.0x	32,848	34,241
2	Two or more prescription fills for OAA to manage MM		
	Thalidomide, lenalidomide, and pomalidomide	6,656	8,590
3	Eligibility criteria		
	Continuous enrollment in medical and prescription drug benefits 1-year pre- and post-OAA initiation	1,699	3,372
	Medicare eligible because of age or disability (exclude ESRD)	NA	3,370
4	Excluding patients with additional cancer diagnosis for chronic myeloid or chronic lymphocytic leukemia	1,699	3,365
5	Prescription utilization for chronic conditions		
	Two or more prescription fills for comorbid conditions 1-year preindex and 1-year postindex date		
	Type 2 diabetes	160	421
	Hypertension	689	2,093
	Hyperlipidemia	287	1,042
6	Medical diagnosis for chronic conditions		
	At least one diagnosis for comorbid conditions in the pre- or postperiod		
	Type 2 diabetes	152	392
	Hypertension	651	1,892
	Hyperlipidemia	250	887
7	Multiple chronic condition requirement		
	Any diagnosis for any additional Elixhauser chronic condition in either the pre- or postperiod		
	Type 2 diabetes	151	380
	Hypertension	646	1,828
	Hyperlipidemia	249	872
8	Pre-exclusion criteria cohort	732	2,040
9	Exclusion criteria		
	Age < 18 years at index	0	0
	Comorbid HIV (ICD-9: 042-044.9, V08, 795.71 or ICD-10: B20-B24)	4	3
	Stem-cell transplant within 1 year of OAA initiation	143	172
10	Final analytical sample size	585	1,865

Abbreviations: CCAE, Commercial Claims and Encounters; ESRD, End-Stage Renal Disease; ICD-9, International Classification of Disease, ninth revision; ICD-10, International Classification of Disease, 10th revision; MM, multiple myeloma; NA, not available; OAA, oral anticancer agent.

20.2 (SD = 9.69) among nonadherent patients compared with 18.7 (SD = 8.73) among adherent patients ($P < .001$).

Finally, DiD models determined whether nonadherence to OAA treatments was a predictor of lower adherence rates for medications used to manage comorbid diabetes, hypertension, or hyperlipidemia among patients with multiple chronic conditions (Table 3). Nonadherence to OAA medications was a significant predictor of reductions in adherence to antihypertensive medications in both unadjusted and multivariate-adjusted models in both the CCAE and Medicare samples. Following covariate adjustment, nonadherent OAA users in Medicare experienced a 2.5% greater decline in antihypertensive medication adherence after OAA initiation than the year before relative to patterns of antihypertensive adherence observed over the same period in patients adherent to OAA treatment. Similarly, interpreting the DiD estimate for CCAE users suggests a 5.2% reduction in adherence after OAA initiation among nonadherent antihypertensive medication users. It should be noted that in unadjusted models, adherence to statins among Medicare patients trended lower in nonadherent OAA users relative to patients who adhered to OAA treatment. However, these results were not statistically significant after multivariate covariate adjustment for potential confounding variables.

DISCUSSION

This claims-based analysis using two large, nationally representative databases uncovered the potential for multiple forms of medication nonadherence among adults initiating oral therapy for MM. Specifically, initial OAA adherence among patients with MM was suboptimal in both commercially insured and Medicare populations, and this

TABLE 2. Comparison of Population Characteristics Between Adherent and Nonadherent OAA Users

	CCAE Sample			Medicare 20% Random Sample		
	OAA Adherence			OAA Adherence		
Characteristic	Adherent (PDC ≥ 80%; n = 141) No. (%)	Nonadherent (PDC < 80%; n = 444) No. (%)	*P*	Adherent (PDC ≥ 80%; n = 780) No. (%)	Nonadherent (PDC < 80%; n = 1,085) No. (%)	*P*
Mean age, years (SD)	58.2 (5.0)	57.6 (5.2)	.253	74.1 (7.05)	74.4 (7.95)	.554
Sex						
Male	91.0 (64.5)	259.0 (58.3)	.190	372.0 (47.70)	549.0 (50.60)	.216
Female	50.0 (35.5)	185.0 (41.7)		408.0 (52.30)	536.0 (49.40)	
Region						
Northeast	27.0 (19.2)	96.0 (21.6)	.486	152.0 (19.40)	213.0 (19.60)	.636
Midwest[a]	22.0 (15.6)	90.0 (20.3)		190.0 (24.40)	263.0 (24.20)	
South	75.0 (53.2)	211.0 (47.5)		118.0 (15.10)	153.0 (14.10)	
West	17.0 (12.1)	47.0 (10.6)		320.0 (41.00)	453.0 (41.80)	
Others	—	—		0.0 (0.00)	3.0 (0.30)	
Urban MSA	122.0 (86.5)	381.0 (85.8)	.832	618.0 (79.20)	836.0 (77.10)	.295
Chronic conditions						
Hypertension	133.0 (94.3)	419.0 (94.4)	.985	725.0 (92.90)	1,036.0 (95.50)	.019
Type 2 diabetes	57.0 (40.4)	165.0 (37.2)	.487	278.0 (35.60)	483.0 (44.50)	< .001
Hyperlipidemia	97.0 (68.8)	278 (62.6)	.183	533.0 (68.30)	790.0 (72.80)	.036
Elixhauser condition count (SD)	6.3 (2.7)	7.0 (2.8)	.012	6.7 (3.00)	8.1 (3.35)	< .001
Count of therapeutic drug classes (SD)	13.9 (6.1)	12.7 (5.7)	.038	18.7 (8.73)	20.2 (9.69)	< .001
Mean inpatient visits (SD)	0.8 (0.6)	0.7 (0.6)	.627	0.8 (1.01)	0.8 (1.19)	.259
Mean outpatient visits (SD)	43.7 (24.8)	33.7 (23.7)	< .001	15.1 (13.90)	15.6 (14.61)	.471
Mean ER visits (SD)	0.7 (1.1)	0.6 (1.2)	.742	0.7 (1.25)	0.8 (1.25)	.079
Mean OAA co-pay (SD), $, USD	230.6 (834.9)	198.1 (644.9)	.672	1,354.3 (1,269.94)	1,257.4 (1,255.25)	.162

Abbreviations: CCAE, IBM Truven Commercial Claims and Encounters Data Source; ER, emergency room; MSA, metropolitan statistical area; OAA, oral anticancer agent; PDC, proportion of days covered; SD, standard deviation; USD, US dollars.

[a]Midwest region is used in Medicare, whereas the North Central region is used in CCAE.

TABLE 3. Difference-in-Differences Models Comparing the Change in Adherence for Comorbid Conditions by Oral Anticancer Agent Adherence (≥ 80%) Status Among Adults With Multiple Myeloma

Medicare 20% Random Sample Cohort[a]

		Comorbid Medication Adherence		Difference-in-Differences	
Comorbid Medication Use Cohorts	**OAA Adherence Cohorts (adherence = PDC ≥ 80%)**	**Baseline Mean Comorbid Medication Adherence (PDC)**	**Follow-Up Mean Comorbid Medication Adherence (PDC)**	**Unadjusted**	**Adjusted**
Oral antidiabetic medications	Adherent (n = 138)	87.9 (85.2-90.6)	87.2 (84.0-90.5)	–3.8% (*P* = .101)	–2.8% (*P* = .212)
	Nonadherent (n = 219)	86.0 (83.9-88.1)	81.5 (78.9-84.0)		
Antihypertensive medications	Adherent (n = 683)	91.1 (90.1-92.2)	89.8 (88.4-91.1)	–2.9% (*P* = .003)	–2.5% (*P* = .013)
	Nonadherent (n = 990)	90.8 (89.9-91.7)	86.6 (85.4-87.7)		
Statins	Adherent (n = 329)	85.7 (84.0-87.3)	85.6 (83.6-87.6)	–3.6% (*P* = .013)	–2.8% (*P* = .069)
	Nonadherent (n = 468)	86.1 (84.7-87.4)	82.4 (80.7-84.0)		

Commercial Claims and Encounters Cohort[b]

		Comorbid Medication Adherence		Difference-in-Differences	
Comorbid Medication Use Cohorts	**OAA Adherence Cohorts (adherence = PDC ≥ 80%)**	**Baseline Mean Comorbid Medication Adherence (PDC)**	**Follow-Up Mean Comorbid Medication Adherence (PDC)**	**Unadjusted**	**Adjusted**
Oral antidiabetic medications	Adherent (n = 35)	89.1 (12.7)	79.7 (25.5)	3.2% (*P* = .505)	1.4% (*P* = .797)
	Nonadherent (n = 85)	81.1 (20.0)	75.3 (24.8)		
Antihypertensive medications	Adherent (n = 126)	91.3 (12.2)	91.3 (13.2)	–5.7% (*P* = .016)	–5.2% (*P* = .031)
	Nonadherent (n = 388)	87.0 (16.7)	81.3 (22.5)		
Statins	Adherent (n = 55)	86.0 (15.0)	84.1 (20.6)	–5.7% (*P* = .152)	–4.4% (*P* = .286)
	Nonadherent (n = 144)	81.9 (17.6)	74.3 (24.5)		

Abbreviations: OAA, oral anticancer agent; PDC, proportion of days covered.

[a]Medicare model adjusts for age, sex, race, region, urban residence, Elixhauser condition sum, therapeutic drug count, and index co-pay amount.

[b]Commercial Claims and Encounters model adjusts for age, sex, region, urban residence, Elixhauser condition sum, therapeutic drug count, and index co-pay amount.

behavior appeared to influence the use of medications for pre-existing comorbid conditions, with consistent significant declines observed among adults on antihypertensive therapy. In addition, although less consistent, results suggested that some changes in adherence to antidiabetic or lipid-lowering medications could be expected among patients with MM who are initially nonadherent to OAA treatments. It is especially concerning that adherence to diabetes medications was noted to decrease after initiation of an OAA, at least in Medicare patients (despite not achieving thresholds for statistical significance). Dexamethasone remains a cornerstone of MM treatment and is used in combination with OAAs, but a common adverse effect of this corticosteroid therapy is steroid-induced hyperglycemia. Therefore, it would be of even greater importance that patients remain adherent to their diabetes regimen while taking OAAs with dexamethasone to help prevent or offset the diabetogenic effects of these myeloma therapies.

The OAA adherence rates identified in this study are alarmingly low and dramatically different by group, at 24.1% in the CCAE cohort and 38.4% in the Medicare cohort. This is of major concern considering the degree to which strict adherence is associated with disease outcomes. For example, in a study evaluating the difference in the 6-year probability of achieving a major molecular response with imatinib treatment in chronic myelogenous leukemia, patients who had a 90% or higher adherence rate had a 94.5% major molecular response rate compared with only a 28.4% rate in patients who were < 90% adherent.[21] However, despite the low rates observed in this study, the results are consistent with previously published findings on OAA adherence rates in MM, which were as low as 58%.[7-11] There may be many significant factors contributing to low OAA adherence in this study, including medication cost, side effects, or lack of understanding of the treatment regimen.[12,13] However, the current study demonstrates that a patient's overall daily pill burden may also play a role in decreased adherence rates. As was noted in both samples, those who were nonadherent to OAA medications also tended to have higher disease and treatment burdens and more comorbid conditions. This is a key potential area of intervention for providers to help improve their counseling techniques and better address all potential adherence barriers.

This study adds to existing evidence that the initiation of cancer treatments can reduce adherence to medications used to manage comorbid chronic conditions.[22] The

importance of chronic disease management in patients with cancer has been well documented and has created a need for improved communication between primary care providers and oncology specialists.[23-25] The current study further confirms this need in a cancer population at high risk of chronic disease complications when the cancer treatment or cancer itself has a propensity for worsening the control of the chronic disease as is the case in MM.[26,27] In addition, it is known that the increasing presence of comorbidities in a patient with MM is associated with a decrease in survival.[28] Given this information and the above findings related to alarmingly low adherence rates, the importance of enhanced interdisciplinary and coordinated care in this high-risk patient population should be emphasized. Specifically, for Medicare members, employment of a comprehensive geriatric assessment is one such approach that would take into consideration pertinent risks for these patients and draw upon the expertise of multiple disciplines (eg, pharmacists related to polypharmacy and optimizing medication management, physical therapists to assess fall risks and optimize functional status, etc) to optimize treatment outcomes.[29,30] Stark differences in adherence between Medicare members and working-age adults with commercial insurance draw attention to the potential for a wide variation in medication use by payer type. One explanation for this phenomenon is the influence of recent emphasis placed on adherence in target conditions in Medicare populations, potentially spilling over into OAA treatment. This is not to say that the importance of adherence to therapy is not stressed among commercially insured adults, but rather that Medicare quality measures focused on improving medication use have demonstrated a significant impact in chronic diseases, whereas similar concerted efforts in younger populations are less consistent.[31] The availability of robust patient-level factors across databases limited this study in exploring this disparity in more detail; therefore, future investigations should consider identifying specific patient characteristics or beliefs and attitudes that may be contributing to such a wide variation.

This study was limited in several ways, mostly related to the characteristics of the data used. First, the analyses relied on assessing adherence using administrative claims, which requires an indirect measurement of medication use. Although PDC is a widely used and accepted measure of adherence, it only accounts for medication on hand, and the calculations do not necessarily reflect actual medication use. In addition, administrative claims carry additional limiting characteristics, such as potential miscoding, missing data, and cancer staging. Second, both MarketScan and the Medicare databases have only a limited set of information on patients available for analysis; therefore, adjusted models were limited to controlling for only a select number of factors that could be contributing to OAA and chronic disease medication use. Finally, the databases used capture the resource utilization of those with insurance coverage, through either commercial plans or fee-for-service Medicare; therefore, results may not be generalizable to populations with other types of coverage (eg, Medicaid) or those without insurance.

In conclusion, adherence to OAAs prescribed to treat MM in adults remains problematic, particularly among those with high disease or treatment burden. Considering the likelihood of adults with MM having comorbid conditions, providers must be cognizant of the potential relationship between adherence to OAAs and medications for preexisting diseases. Results suggest that monitoring of medication use among patients with MM with multiple chronic conditions who are starting OAA therapy should not be limited solely to ensuring adherence to the anticancer agent. Rather, the starting of OAA therapy provides an opportunity for all involved practitioners to reinforce the importance of total regimen adherence to improve the odds of positive cancer- and noncancer-related outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Medication Adherence Among Adults With Comorbid Chronic Conditions Initiating Oral Anticancer Agent Therapy for Multiple Myeloma

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