3-1-2020

Disease-modifying therapy adherence and associated factors in a national sample of Medicare patients with multiple sclerosis

Pengxiang Li

Vrushabh P Ladage

Joseph Berger

Salim Chahin

Mehul Jhaveri

See next page for additional authors

Authors

Pengxiang Li, Vrushabh P Ladage, Joseph Berger, Salim Chahin, Mehul Jhaveri, Caroline Geremakis, and Jalpa A Doshi

ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Health Policy Analysis

Disease-Modifying Therapy Adherence and Associated Factors in a National Sample of Medicare Patients With Multiple Sclerosis

Pengxiang Li, PhD,[1] Vrushabh P. Ladage, MHCI,[1] Joseph Berger, MD,[1] Salim Chahin, MD,[2] Mehul Jhaveri, PharmD,[3] Caroline Geremakis, PhD,[4] Jalpa A. Doshi, PhD[1,*]

[1]Division of General Internal Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [3]Global Value and Access, Biogen, Cambridge, MA, USA; [4]Medical Value Strategy and Execution, Biogen, Weston, MA, USA.

ABSTRACT

Objectives: Disease-modifying therapies (DMTs) reduce relapse rates and disability progression for relapsing multiple sclerosis (MS). Although 25% to 30% of all US patients with MS are Medicare beneficiaries, limited information exists on this population. This is the first study using national Medicare data to (1) describe characteristics of patients with MS using DMTs, (2) estimate adherence to DMTs over a 1-year and 3-year follow-up, and (3) examine factors associated with DMT adherence.

Methods: This retrospective claims analysis used 2011-2014 100% Medicare files. Monthly adherence to MS DMTs was defined as the proportion of days covered ≥0.80 with any DMT in each month for 1-year (n = 36 593) and 3-year (n = 17 599) follow-up samples of MS DMT users. Generalized estimating equation logistic regressions were used to estimate factors associated with adherence to DMTs.

Results: Over 90% of patients were eligible for Medicare owing to disability, and about three-quarters qualified for low-income subsidies. A downward trend in DMT adherence was observed over time in both samples. Monthly adherence dropped significantly between December of the prior year to January of the following year (from 76% to 65% in the 1-year follow-up sample and similar drops seen across all years in the 3-year follow-up sample). Multivariable regressions indicated characteristics such as being low-income, having a disability, and having high patient out-of-pocket DMT costs associated with poor adherence to DMTs.

Conclusion: Our study provides important insights into the characteristics and DMT adherence of Medicare patients with MS and highlights the need for interventions and policies mitigating barriers to adherence in this population.

Keywords: adherence, administrative claims data, disease-modifying therapies, multiple sclerosis, Medicare.

VALUE HEALTH. 2020; 23(3):328–334

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, disabling autoimmune disease of the central nervous system affecting approximately 1 million Americans.[1,2] Approximately 85% of individuals with MS are initially diagnosed with the relapsing-remitting form of the disease, which is characterized by acute exacerbations or relapses (eg, problems with vision, balance, gait, or speech).[3,4] Although there exists no curative treatment for relapsing-remitting MS, disease-modifying therapies (DMTs) have been shown to reduce relapse rates, slow disease progression, and delay disability; thereby constituting the primary treatment for relapsing forms of MS.[5] Achieving therapeutic goals through DMTs requires patients to be adherent to their prescribed therapy. As with most therapies for chronic conditions, patient adherence to DMTs has been reported to be suboptimal in the United States.[6] Nevertheless, most of these studies have been conducted in privately insured patients.[6-13]

Limited information exists on patients with MS covered by Medicare, a federally funded health insurance program for elderly individuals or individuals with a disability in the United States. This is a glaring gap in the literature because it has been estimated that 25% to 30% of all patients with MS in the United States are covered under Medicare.[14-16] There are several additional reasons to examine the Medicare patients with MS. Medicare patients are typically excluded from MS clinical trials of DMTs owing to their age or disability. Hence, a better understanding of the characteristics of Medicare patients with MS who are using DMTs and their real-world treatment utilization patterns is an important first step prior to evaluation of clinical outcomes associated with DMT use

* Address correspondence to: Jalpa A. Doshi, PhD, Blockley Hall, Room 1223 423 Guardian Dr, Philadelphia, PA 19104 Email: jdoshi@pennmedicine.upenn.edu

https://doi.org/10.1016/j.jval.2019.10.011

in this population. In addition, unlike privately insured patients, once enrolled, patients are covered under Medicare throughout their lifetime. Thus, identification of suboptimal adherence and associated factors has the potential to inform targeting of Medicare policies and quality improvement efforts to improve long-term clinical outcomes (eg, disability progression) and healthcare spending in this population.

This study is the first to use data from a national sample of Medicare patients to (1) describe characteristics of beneficiaries with MS using DMTs; (2) estimate adherence to DMTs over a 1-year and 3-year longitudinal follow-up; and 3) examine demographic, clinical, and policy-related factors associated with MS DMT adherence.

Methods

Data Source

Data on patients with MS using DMTs at any time during 2011 to 2014 were extracted from the Chronic Conditions Data Warehouse 100% Medicare files available from the Centers for Medicare & Medicaid Services. The Chronic Conditions Data Warehouse database includes Medicare Part A and Part B medical claims for inpatient care, skilled nursing facility care, home health services, outpatient services, durable medical equipment, and hospice services as well as Part D prescription claims files for outpatient prescription drug events for fee-for-service Medicare beneficiaries. These files were linked to personal summary files that contained patient demographics and eligibility information and Part D plan characteristics files. Part D plan characteristics files included information such as the plan premium, type of plan (eg, Prescription Drug Plans and Medicare Advantage Prescription Drug Plans), and type of benefit (eg, standard, enhanced alternative).

Study Design and Sample

This was a retrospective administrative claims analysis examining patient characteristics and DMT adherence among 1-year and 3-year follow-up samples of patients with MS using DMTs. The DMTs available during the study period and included in the study are listed in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.10.011. The sampling frame consisted of person-year observations of beneficiaries with fee-for-service Medicare coverage who were enrolled in a standalone Part D plan and had evidence of DMT use in any year between 2011 and 2014. Next, we created 2-year segments over any 2 consecutive year period (2011-2012, 2012-2013, 2013-2014) wherein the first year in the 2-year segment was referred to as the baseline year, and the second year was referred to as the follow-up year. Two-year segments for our 1-year follow-up sample were selected for DMT users with 12-month Medicare fee-for-service and standalone Part D coverage and ≥1 inpatient or ≥2 outpatient claims with a diagnosis of MS (*International Classification of Diseases, ninth revision, Clinical Modification* code 340.xx) in the baseline year who additionally met the following criteria: (1) ≥1 claim for any DMT in the last quarter of the baseline year to ensure recent use before the follow-up period for measuring outcomes, (2) 12-month continuous fee-for-service Medicare and Part D coverage and alive in the follow-up year, (3) not in hospice in the follow-up year, (4) with 12-month full low-income subsidy (LIS) or non-LIS (Medicare beneficiaries not qualifying for Part D LIS) status in the follow-up year, and (5) with no missing data points or covariates necessary for the study. For each patient, the earliest 2-year segment for which they met eligibility criteria was selected for inclusion in the final 1-year follow up sample. For example, if patients met the eligibility criteria for three 2-year segments (2011-2012, 2012-2013, and 2013-2014), only 2011-2012 segment was selected. The 3-year follow-up sample was a subsample of our 1-year follow-up sample with an additional requirement of continuous 3-year Medicare fee-for-service and standalone Part D coverage during the follow-up period.

Outcome Measures

The primary outcome of interest was monthly adherence to any MS DMT, which allows examination of changes in adherence by month. Monthly adherence to the MS DMTs was defined as the proportion of days covered (PDC) with any DMT (Part B or Part D) in each month.[12] The PDC was measured as the number of days covered with any DMT divided by a fixed time interval (eg, 30 days) from the start of the period (eg, the first date of a month). For example, a patient with MS having DMT coverage available for 24 days during the 30-day period would have a PDC of 24/30 = 0.80. A PDC ≥ 0.80 was deemed as adherent.[17,18] In sensitivity analysis, we defined adherence as PDC ≥ 0.7 or PDC ≥ 0.9. The DMTs for MS that are infused or administered under medical supervision (eg, natalizumab) fall under Medicare's Part B medical benefit and do not have a "days' supply" data field. Therefore, the days' supply for Part B DMTs was assigned using its recommended dosage regimen.[19] Additionally, the PDC was adjusted to not account for the days of hospital or skilled nursing facility stay in its calculation to avoid underestimating PDC among such patients.[20] Thus, any day a patient spent in a hospital or skilled nursing facility was removed from the numerator and denominator of the PDC because patients may have received their medication in the facility.

Covariates

The covariates of interest in this study included a set of sociodemographic, clinical, and Part D plan benefit-related variables. Sociodemographic variables included Medicare entitlement reason (aged ≥65 years, aged ≥65 years but originally eligible as disabled, and disabled under age 65 years), beneficiary age, sex, race/ethnicity, census region of residence, and per-capita income in the beneficiary's county of residence. Clinical variables included the prescription drug hierarchical condition category (RxHCC) risk score,[21] which has been used to adjust for potential selection biases in drug use studies among Medicare patients,[22,23] and the presence of any all-cause hospitalization in the baseline year. Specific variables related to MS clinical burden were also measured, including the number of MS symptoms (bowel dysfunction, cognitive dysfunction, depression or anxiety, double vision, fall, fatigue, gait dysfunction, chronic pain, seizures, spasticity, tremor, urinary incontinence, vision loss, etc), use of assistive devices for mobility identified from the durable medical equipment claims, and number of MS relapses[24] in the baseline year. In addition, our models included indicators for index year (1-year follow-up model) or the follow-up year (3-year follow-up model). Part D prescription drug plan benefit-related variables included Medicare Part D plan type (defined standard benefit, actuarially equivalent standard, basic alternative, and enhanced alternative), Medicare Part D LIS status (full LIS vs non-LIS), and Part D benefit phase defined by level of cost sharing (ie, patient out-of-pocket costs). For the latter, each person-month observation was coded as being in a high Part D cost-sharing phase (ie, deductible, initial coverage, or coverage gap phase) or low Part D cost-sharing phase (ie, catastrophic phase). Owing to the Part D subsidy, full LIS patients face substantially lower out-of-pocket costs than non-LIS patients in all Part D cost-sharing phases.[20]

Given the differences in the levels of cost sharing between these groups, the regression models also included a covariate for an interaction term between Part D low-income subsidy status and Part D cost-sharing phase.

Statistical Analysis

Descriptive sample characteristics for the 1-year and 3-year follow-up samples were generated. The proportion of patients adherent (PDC ≥ 0.80) to any DMT in each month was plotted over 1-year and 3-year follow-up. Multivariable generalized estimating equation logit regressions adjusting for repeated measures were used to examine factors associated with being adherent to any DMT using the person-month data for the 1-year and 3-year follow-up sample. In addition, we conducted 2 sets of subgroup analyses, namely among patients who had an MS relapse in the baseline year and patients who had a disability under age 65 years. We also conducted a series of sensitivity analyses. We reran models based on 2 alternative definitions of being deemed adherent (PDC ≥ 0.70 or PDC ≥ 0.90 instead of PDC ≥ 0.80 in the main analysis). Additional sensitivity analyses were conducted wherein the outcome variable was re-specified as adherence to Part D–covered DMTs (as opposed to any [Part D– or Part B–covered] DMTs in the main analysis). All models accounted for clustering owing to repeated observations per patient. The blinded institutional review board deemed the study exempt from informed consent procedures because no data were collected directly from patients.

Results

The final sample with at least 1 year of follow-up consisted of 36 593 patients with MS using any DMT (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.10.011). Within our 1-year follow-up sample, 18% were elderly, of which half were originally entitled to Medicare owing to disability but were now over age 65 (Table 1). The remaining 82% of the sample were those with a disability aged under 65, with most between ages 45 and 64. The sample was predominantly female (77%) and white (79%). In clinical characteristics, almost one-quarter of the sample had an all-cause hospitalization, 18% had a claim for 1 or more assistive devices for mobility needs, and 26% had at least 1 MS relapse in the baseline year. Most patients were enrolled in an actuarially equivalent standard benefit plan or basic alternative plan under Medicare Part D. About 72% of our sample qualified for full LIS status under Medicare Part D. On average, full LIS patients paid $4 and $0, and non-LIS patients paid $1338 and $220 per 30-day supply of Part D DMTs in the high cost-sharing and low-cost sharing phases, respectively (data not shown). Similar characteristics were reported in the 3-year follow-up sample (n = 17 599, Table 1).

Figure 1 presents the percentage of patients adherent to MS DMTs for each month in the 1-year and 3-year follow-up samples. A significant drop in rates of being adherent was observed in January (from 76% in December of baseline year to 65% in the 1-year follow-up sample, and 78% in December of baseline year to 67% in the first year of the 3-year follow-up sample). Similarly, drops were observed consistently between December and January even for the second and third years of follow-up in the 3-year follow-up sample. Although adherence rates climbed in February, they did not reach the levels observed in the months before January. In addition, there was a downward trend of DMT adherence in the 3-year follow-up sample (annual adherence rates dropped from 64% in first year to 59% in the third year; data not shown).

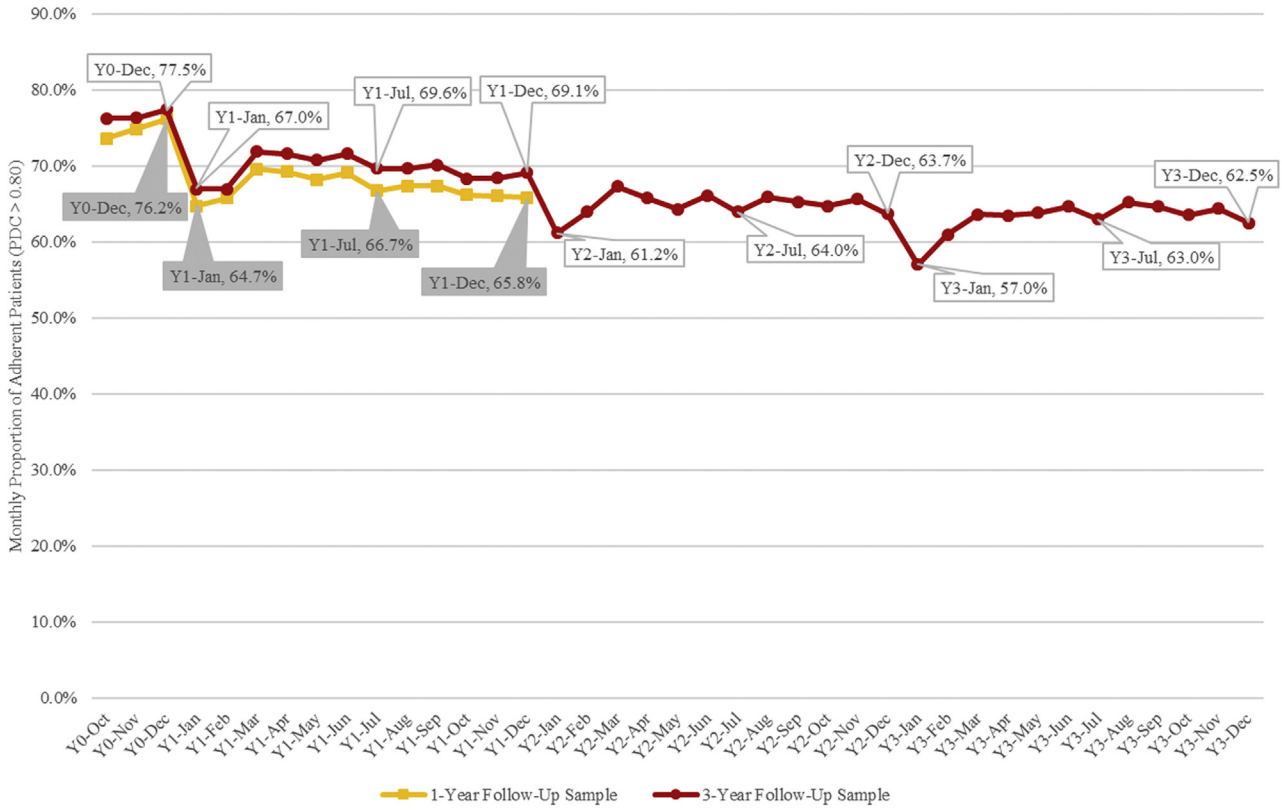
Table 1. Sample characteristics of Medicare beneficiaries with multiple sclerosis using disease-modifying therapies.

Factors	1-year follow-up sample (n = 36 593)	3-year follow-up sample (n = 17 599)
Sociodemographic characteristics		
Age, mean (SD)	52.0 (11.8)	52.2 (11.6)
Medicare entitlement reason (%)		
Aged ≥65, original entitlement to Medicare not due to disability	3311 (9)	1409 (8)
Aged ≥65, original entitlement to Medicare due to disability	3235 (9)	1624 (9)
Disabled under age 65 y	30 047 (82)	14 566 (83)
<34 y	2925 (8)	1284 (7)
35-44 y	7074 (19)	3319 (19)
45-54 y	11 044 (30)	5447 (31)
55-64 y	9004 (25)	4516 (26)
Sex (%)		
Female	28 072 (77)	13 616 (77)
Male	8521 (23)	3983 (23)
Race (%)		
White	28 955 (79)	14 150 (80)
Black	5809 (16)	2575 (15)
Latino and others	1829 (5)	876 (5)
Region (%)		
Northeast	8078 (22)	4159 (24)
Midwest	10 503 (29)	5050 (29)
South	11 997 (33)	5575 (32)
West	6015 (16)	2815 (16)
Per-capita income in $10 000s in county of residence, mean (SD)	4.2 (1.1)	4.1 (1.1)
Clinical characteristics		
RxHCC, mean (SD)	1.7 (0.4)	1.7 (0.4)
Any inpatient stay in baseline year (%)	8491 (23)	3996 (23)
Number of multiple sclerosis symptoms, mean (SD)	2.2 (1.8)	2.2 (1.8)
Use of assistive device(s) for mobility (%)	6424 (18)	3130 (18)
Number of relapses in baseline year, %		
0	27 119 (74)	13 071 (74)
1	6305 (17)	2969 (17)
≥2	3169 (9)	1559 (9)
Part D prescription benefit characteristics		
Part D plan type (%)		
Actuarially equivalent standard	16 062 (44)	6973 (40)
Basic alternative	11 018 (30)	6202 (35)
Defined standard benefit	3343 (9)	1947 (11)
Enhanced alternative	6170 (17)	2477 (14)
Part D LIS status (%)		
Full LIS	26 429 (72)	13 168 (75)
Non-LIS	10 164 (28)	4431 (25)

Note. All patients in 3-year follow-up sample have index year of 2012. Data source: 2011-2014 Chronic Conditions Data Warehouse 100% Medicare files. Data are n (%) or mean (SD).
LIS indicates low-income subsidies under Medicare Part D; RxHCC, prescription drug hierarchical condition category risk score.

The multivariable analysis of factors associated with being adherent is shown in Table 2. In the 1-year follow-up sample, several sociodemographic factors were associated with the odds of being adherent. Disability as the current or original Medicare entitlement reason was associated with lower odds of being adherent across all age categories. Men had higher odds than women (OR 1.15; 95% CI:1.11-1.19), and black patients had lower

Figure 1. Proportion of Medicare beneficiaries with multiple sclerosis adherent (PDC ≥ 0.80) to any disease-modifying therapy in each month of follow-up (1-year and 3-year follow-up samples).



PDC indicates proportion of days covered.

odds of being adherent compared to white patients (OR 0.92; 95% CI: 0.89-0.96). For clinical factors, patients with a higher RxHCC score and having an inpatient stay in the baseline year had lower odds of being adherent. Interestingly, patients with MS relapses in the baseline year had lower odds of being adherent in the follow-up year. For Part D benefit design factors, patients in plans with the standard Part D benefit or plans that offered a basic alternative or actuarially equivalent to standard benefit design had lower odds of being adherent than patients in the more generous enhanced alternative Part D plans. Being in the high cost-sharing phase was associated with lower odds of being adherent than in the low cost-sharing phase. Although non-LIS status under Medicare Part D was associated with higher odds of being adherent than LIS status during the low cost-sharing phase (OR 1.47; 95% CI: 1.41-1.54), the high cost-sharing phase had a larger negative impact on non-LIS patients than on LIS patients as evidenced by the statistically significant lower odds ratio on the interaction term (OR 0.55; 95% CI: 0.53-0.57).

Multivariable analysis of the 3-year follow-up sample had similar results as those observed in the 1-year follow-up sample with the exception that the Medicare entitlement reasons and race no longer had statistically significant associations with the odds of being adherent (Table 2). Of note with this longitudinal sample was the decline in adherence over the 3 years of follow-up as evidenced by the result that patients had lower odds of being adherent during the second year (OR 0.82; 95% CI:0.81-0.83) and third year (OR 0.75; 95% CI: 0.74-0.76) of follow-up compared to the first year.

Consistent with main results, our subgroup analysis of patients with an MS relapse in the baseline year (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.10.011) and patients with a disability under age 65 years (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.10.011) and all our sensitivity analysis (see Appendix Tables 4 and 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.10.011) found that male and non-LIS statuses were associated with higher adherence and a higher RxHCC score, and being in the high cost-sharing phase was associated with lower odds of being adherent than in the low cost-sharing phase. Also, the high cost-sharing phase had a larger negative impact on non-LIS patients than on LIS patients as evidenced by the statistically significant lower odds ratio on the interaction term.

Discussion

This study is among the first to profile the characteristics of a national sample of fee-for-service Medicare beneficiaries with MS using DMTs and examine treatment adherence and associated factors over longitudinal follow-up. An examination of this relatively large group of patients with MS in the United States was important because compared to their commercially insured counterparts, this group is primarily composed of low-income individuals with a disability. About nine out of ten Medicare beneficiaries in our study were currently or previously eligible for Medicare owing to disability (ie, after receiving disability benefits from the Social Security Administration for at least 2 years). Contrary to the common belief that Medicare patients with MS are typically 65 years or older, our study finds that eight out of

Table 2. Factors associated with being adherent (PDC ≥ 0.80) to any disease-modifying therapy among Medicare beneficiaries with multiple sclerosis (1-year and 3-year follow-up sample).

Factors	1-year follow-up sample		3-year follow-up sample	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sociodemographic characteristics				
Medicare entitlement reason				
Aged ≥65, original entitlement to Medicare not due to disability	1.00 (ref)	-	1.00 (ref)	-
Aged ≥65, original entitlement to Medicare due to disability	0.91 (0.85-0.98)	.007	0.99 (0.91-1.08)	.793
Disabled under age 65 y				
<34 y	0.78 (0.72-0.84)	<.0001	0.97 (0.88-1.06)	.486
35-44 y	0.82 (0.77-0.87)	<.0001	1.00 (0.92-1.08)	.923
45-54 y	0.87 (0.82-0.93)	<.0001	1.01 (0.94-1.09)	.791
55-64 y	0.93 (0.88-0.98)	.010	1.05 (0.97-1.13)	.228
Sex				
Female	1.00 (ref)	-	1.00 (ref)	-
Male	1.15 (1.11-1.19)	<.0001	1.14 (1.09-1.19)	<.0001
Race				
White	1.00 (ref)	-	1.00 (ref)	-
Black	0.92 (0.89-0.96)	<.0001	0.97 (0.92-1.02)	.174
Latino and others	0.97 (0.91-1.04)	.381	0.98 (0.91-1.06)	.644
Region				
Northwest	1.00 (ref)	-	1·00 (ref)	-
Midwest	0.98 (0.94-1.02)	.322	0.96 (0.92-1.01)	.129
South	0.98 (0.94-1.02)	.251	0.95 (0.91-1.00)	.064
West	0.96 (0.92-1.00)	.068	0.97 (0.91-1.02)	.262
Per-capita income in $10 000s in county of residence, mean (SD)	1.00 (0.99-1.01)	.835	1.01 (1.00-1.03)	.092
Clinical characteristics				
RxHCC score	0.86 (0.83-0.89)	<.0001	0.90 (0.86-0.94)	<.0001
Any inpatient stay in baseline year	0.84 (0.81-0.87)	<.0001	0.88 (0.84-0.92)	<.0001
Total count of multiple sclerosis symptoms	1.00 (0.99-1.01)	.862	0.98 (0.97-0.99)	<.0001
Use of assistive device(s) for mobility	1.01 (0.98-1.05)	.441	0.98 (0.94-1.03)	.472
Number of relapses in baseline year				
0	1.00 (ref)	-	1.00 (ref)	-
1	0.96 (0.92-0.99)	.021	0.97 (0.92-1.01)	.158
≥2	0.87 (0.83-0.91)	<.0001	0.88 (0·83-0·94)	<.0001
Part D prescription benefit characteristics				
Part D plan type				
Actuarially equivalent standard	0.94 (0.90-0.98)	.006	0.95 (0.89-1.00)	.069
Basic alternative	0.94 (0.90-0.98)	.007	0.95 (0.90-1.00)	.068
Defined standard benefit	0.89 (0.84-0.94)	<.0001	0.92 (0.86-1.00)	.036
Enhanced alternative	1.00 (ref)	-	1.00 (ref)	-
Part D LIS status				
Full LIS	1.00 (ref)	-	1.00 (ref)	-
Non-LIS	1.47 (1.41-1.54)	<.0001	1.5 (1.42-1.59)	<.0001
Part D cost sharing phase				
Low cost-sharing phase	1.00 (ref)	-	1·00 (ref)	-
High cost-sharing phase	0.36 (0.35-0.36)	<.0001	0.31 (0.30-0.31)	<.0001
Interaction term for Part D LIS status and cost-sharing phase				
Non-LIS* high cost-sharing phase	0.55 (0.53-0.57)	<.0001	0.57 (0.56-0.59)	<0.0001
Index year				
2012	1.00 (ref)	-	N/A	N/A
2013	0.89 (0.86-0.93)	<.0001	N/A	N/A
2014	0.86 (0.82-0.89)	<.0001	N/A	N/A
Follow-up year				
1st year of follow-up	N/A	N/A	1.00 (ref)	-
2nd year of follow-up	N/A	N/A	0.82 (0.81-0.83)	<.0001
3rd year of follow-up	N/A	N/A	0.75 (0.74-0.76)	<.0001

Note. All patients in 3-year follow up sample have index year of 2012. Data source: 2011-2014 Chronic Conditions Data Warehouse 100% Medicare files.
LIS indicates low-income subsidies under Medicare Part D; RxHCC, prescription drug hierarchical condition category risk score.
*PDC greater than or equal to 0.80 was deemed as adherent.

ten patients in the study were individuals with a disability younger than age 65. Furthermore, three-quarters of the patients qualified for low-income subsidies under Medicare Part D. The remaining one-quarter of the patients who did not qualify as low-income faced significant out-of-pocket costs for their monthly DMT prescriptions ($220 to $1338). In addition to the high level of disability and financial barriers faced by this population, the burden of MS was also substantial; with one-quarter of the patients having suffered an MS relapse in the baseline year.

Our estimates on DMT adherence are also among the first to be generated in this vulnerable population and highlight that adherence to DMTs in Medicare patients with MS appears to be highly dynamic (and not static) in nature even within a 1-year time frame. An examination of our monthly adherence rates in the 1-year follow-up sample revealed a significant drop in the adherence rate between December of the previous year and January of the following year. Even more noteworthy was the consistent finding of sharp declines in DMT adherence rates from December to January across each of the 3 years in the 3-year follow-up sample. These findings correspond with the transition from the period with the lowest out-of-pocket costs to the period with the highest out-of-pocket costs for DMTs in the year, given the variable design of the annual Medicare Part D benefit (which covers most DMTs), and were confirmed in our multivariable analyses. Although monthly adherence rates increased in February (as the out-of-pocket costs likely became lower in magnitude), it did not return to the level in December of the prior year. Also, regardless of the ups and downs between December and February, adherence rates had an overall declining trajectory over the 3 years of follow-up. These findings suggest that adherence programs and policies should not solely rely on cross-sectional interventions, but rather long-term follow-up is required for sustained DMT adherence in this population. Furthermore, clinicians treating Medicare patients with MS should also be cognizant of this within-year and across-year variability in DMT adherence and inquire about adherence and related issues at each clinic visit.

Our examination of factors associated with MS DMT adherence revealed both expected and novel findings. Consistent with studies examining commercially insured populations,[10,11] we found that being male was associated with higher odds of being adherent to MS DMTs. However, counter to previous studies that have examined relapse as an outcome of nonadherence to DMTs,[6,25-27] our study indicates an association between having an MS relapse in the baseline year and subsequent nonadherence to DMTs in the follow-up years. This is a surprising finding since MS patients with a recent relapse may be more cognizant of the potential severity of the consequences associated with the risk of relapse owing to nonadherence to DMTs, and associated temporary or permanent disability such as weakness, vision loss, or cognitive dysfunction. Nevertheless, it is also likely that the relapse was a consequence of nonadherence in the baseline or prior years and is a proxy for patients who have ongoing problems with DMT adherence. Regardless, these patients represent an important high-risk subgroup to be targeted for understanding barriers to and identifying solutions for adherence to DMTs in daily clinical practice.

Other groups of patients deserving attention that were identified in our study represent underserved populations including minorities (ie, blacks), those with a disability (ie, those qualifying for Medicare due to disability), and low-income (ie, those qualifying for full low-income subsidies under Part D) patients, all of whom were more likely to be non-adherent than their counterparts, despite controlling for other sociodemographic and clinical characteristics.

In addition to identifying several sociodemographic and clinical risk factors for nonadherence that inform targeting of efforts to improve DMT adherence in specific subgroups, our analyses also identified important Part D benefit-related modifiable risk factors. First, Medicare patients with MS who were enrolled in Part D plans with enhanced (ie, generous) benefit designs were more likely to be adherent than those who were enrolled in plans with standard or actuarially equivalent alternative designs. Although this finding could be a result of selection issues wherein patients more likely to be adherent (or in higher need of DMTs) chose enhanced plans, there is strong evidence suggesting most Part D beneficiaries are choosing plans largely based on the monthly premiums.[28,29] Although monthly premiums may be higher for the enhanced plans,[30] other features of these plans (such as supplemental cost-sharing, reduced deductible, or the provision of coverage during the coverage gap/so-called *donut hole*) may result in reduced prescription drug out-of-pocket costs and support better adherence (and clinical outcomes) during the year.[30,31] Hence, there is a critical need for supporting tools and education specifically tailored for patients with MS on the relative costs and benefits of different Part D plan choices during the annual open enrollment period. Second, we found that higher drug out-of-pocket costs were significantly associated with lower monthly DMT adherence rates. Unlike their commercial counterparts, Medicare beneficiaries' cost-sharing requirements under the Part D benefit design fluctuate during the year with out-of-pocket costs highly concentrated at the beginning of the year.[32,33] While the impact of the high cost-sharing phase versus the low cost-sharing phase under Part D was evidently negative even in the full LIS patients who faced an average out-of-pocket cost of $4 versus $0, respectively, it was even more negative in non-LIS patients who faced average out-of-pocket costs of $1338 versus $220, respectively, per 30-day supply of Part D DMTs. These results were even stronger in our sensitivity analysis where we limited the adherence outcome specifically to Part D–covered DMTs, which not only constituted most DMTs used in our sample but also were directly subject to the out-of-pocket costs under the Part D benefit design. Prior work in non-LIS Medicare patients with MS has shown that the month of January represents one-third of the beneficiary's annual Part D out-of-pocket spending on DMTs,[32,33] and the transition from the low cost-sharing phase to the high cost-sharing phase can result in significant DMT treatment interruptions of 30 days or longer (Li et al, 2018).[20] Thus, our findings further add to this evidence base and fuel the call for policy changes to alleviate the total out-of-pocket cost burden under Part D and smooth out these costs over the year, especially for patients needing specialty drugs like DMTs.[32,33] Finally, our results also raise concern for commercially insured patients who are also increasingly facing high deductibles in their health plans and hence will have highly concentrated out-of-pocket costs in the beginning of the year. Future research in these patients is also needed since most studies in privately insured patients are from a period when cost-sharing levels were very low. [22]

Our study findings should be interpreted in light of the following limitations. First, although our PDC measure is a widely used and accepted adherence measurement method with administrative claims datasets,[17] it does not reflect whether a medication was actually taken as prescribed. Second, as is the case with all administrative claims database studies, we did not have information on the reasons for nonadherence to MS DMTs from patients. Third, administrative claims databases are not developed for research purposes and lack information on clinical parameters (eg, disease severity, MS subtype). Hence, we were unable to identify patients in our sample who progressed to secondary progressive MS (which does not require the use of DMTs) over our study period. Nevertheless, oftentimes in clinical practice, neurologists treating patients with MS who become secondary progressive refrain from discontinuing use of DMTs.[34] Fourth, claims data are only available for the Medicare fee-for-service population, and hence the study findings may not be generalizable to Medicare Advantage patients. Lastly, the scope of this study did not include assessing the impact of DMT nonadherence on clinical outcomes, health resource use, and costs. Nevertheless, evidence from privately insured patients suggests that nonadherence to MS

DMTs is associated with an increased risk of relapse and health resource utilization.[35,36] Future research should examine whether similar findings are identified in the Medicare population.

Notwithstanding these caveats, our study provides insights into an important but grossly understudied group of US Medicare patients with MS on DMT therapy with direct implications for clinical practice and policy. Interventions and policies to mitigate barriers to adherence are urgently needed to improve overall DMT adherence and reduce the potentially harmful outcomes of MS relapses and disability progression in this largely underserved population.

Acknowledgments

The authors thank Swathi Raman, BA, for her editorial assistance.

This study was funded by Biogen Inc. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.10.011.

REFERENCES

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372(9648):1502–1517.
2. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: a population-based estimate using health claims data. *Neurology*. 2019;92(10):e1029–e1040.
3. Leary SM, Porter B, Thompson AJ. Multiple sclerosis: diagnosis and the management of acute relapses. *Postgrad Med J*. 2005;81(955):302–308.
4. National Multiple Sclerosis Society. Relapsing-remitting MS (RRMS). https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS. Accessed January 18, 2019.
5. Freedman MS. Present and emerging therapies for multiple sclerosis. *Continuum (Minneap Minn)*. 2013;19(4 Multiple Sclerosis):968–991.
6. Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Adv Ther*. 2011;28(1):51–61.
7. Palmer LA, Fowler R, Shi N, Dastani H, Abouzaid S, Kim E. Impact of patient cost-sharing arrangements for disease modifying therapies on treatment compliance among patients with multiple sclerosis in the United States. *Value Health*. 2011;14(7):A328–329.
8. Reynolds MW, Stephen R, Seaman C, Rajagopalan K. Persistence and adherence to disease modifying drugs among patients with multiple sclerosis. *Curr Med Res Opin*. 2010;26(3):663–674.
9. Kleinman NL, Beren IA, Rajagopalan K, Brook RA. Medication adherence with disease modifying treatments for multiple sclerosis among US employees. *J Med Econ*. 2010;13(4):633–640.
10. Halpern R, Agarwal S, Borton L, Oneacre K, Lopez-Bresnahan MV. Adherence and persistence among multiple sclerosis patients after one immunomodulatory therapy failure: retrospective claims analysis. *Adv Ther*. 2011;28(9):761–775.
11. Bergvall N, Petrilla AA, Karkare SU, et al. Persistence with and adherence to fingolimod compared with other disease-modifying therapies for the treatment of multiple sclerosis: a retrospective US claims database analysis. *J Med Econ*. 2014;17(10):696–707.
12. Dor A, Lage MJ, Tarrants ML, Castelli-Haley J. Cost sharing, benefit design, and adherence: the case of multiple sclerosis. *Adv Health Econ Health Serv Res*. 2010;22:175–193.
13. Johnson KM, Zhou H, Lin F, Ko JJ, Herrera V. Real-world adherence and persistence to oral disease-modifying therapies in multiple sclerosis patients over 1 year. *J Manag Care Spec Pharm*. 2017;23(8):844–852.
14. Owens GM. Economic burden of multiple sclerosis and the role of managed care organizations in multiple sclerosis management. *Am J Manag Care*. 2016;22(6 suppl):s151–158.
15. Mathis AS, Owens GM. Implications for multiple sclerosis in the era of the Affordable Care Act: the shifting managed care landscape. *Am J Manag Care*. 2014;20(11 suppl):242.
16. National Multiple Sclerosis Society. Medicare. https://www.nationalmssociety.org/Living-Well-With-MS/Work-and-Home/Insurance-and-Financial-Information/Health-Insurance/Medicare. Accessed January 18, 2018.
17. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007;10(1):3–12.
18. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):56–57.
19. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in Medicaid enrollees with rheumatoid arthritis. *Value Health*. 2010;13(6):805–812.
20. Li P, Hu T, Yu X, et al. Impact of cost-sharing increases on continuity of specialty drug use: a quasi-experimental study. *Health Serv Res*. 2018;53(suppl 1):2735–2757.
21. Robst J, Levy JM, Ingber MJ. Diagnosis-based risk adjustment for Medicare prescription drug plan payments. *Health Care Financ Rev*. 2007;28(4):15–30.
22. Donohue JM, Morden NE, Gellad WF, et al. Sources of regional variation in Medicare Part D drug spending. *N Engl J Med*. 2012;366(6):530–538.
23. Li P, McElligott S, Bergquist H, Schwartz JS, Doshi JA. Effect of the Medicare Part D coverage gap on medication use among patients with hypertension and hyperlipidemia. *Ann Intern Med*. 2012;156(11):776–784.
24. Chastek BJ, Oleen-Burkey M, Lopez-Bresnahan MV. Medical chart validation of an algorithm for identifying multiple sclerosis relapse in healthcare claims. *J Med Econ*. 2010;13(4):618–625.
25. Steinberg SC, Faris RJ, Chang CF, Chan A, Tankersley MA. Impact of adherence to interferons in the treatment of multiple sclerosis: a non-experimental, retrospective, cohort study. *Clin Drug Investig*. 2010;30(2):89–100.
26. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm*. 2013;19(1 suppl A):S24–40.
27. Lage MJ, Carroll CA, Fairman KA. Using observational analysis of multiple sclerosis relapse to design outcomes-based contracts for disease-modifying drugs: a feasibility assessment. *J Med Econ*. 2013;16(9):1146–1153.
28. Abaluck J, Gruber J. Choice inconsistencies among the elderly: evidence from plan choice in the Medicare Part D program. *Am Econ Rev*. 2011;101(4):1180–1210.
29. Heiss F, Leive A, McFadden D, Winter J. *Plan selection in Medicare Part D: evidence from administrative data*. NBER Working Paper No. 18166; 2012.
30. Kaiser Family Foundation. An overview of the Medicare Part D prescription drug benefit. http://files.kff.org/attachment/Fact-Sheet-An-Overview-of-the-Medicare-Part-D-Prescription-Drug-Benefit. Accessed January 18, 2018.
31. Ingber MJ. Medicare Part D program evaluation: analysis of the impact of Medicare Part D on the FFS program and issues related to medication adherence for six chronic conditions—2008. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Reports/Downloads/Ingber_Part_D_Meds_Adherence_June_2011.pdf. Accessed January 18, 2019.
32. Doshi JA, Li P, Pettit AR, Dougherty JS, Flint A, Ladage VP. Reducing out-of-pocket cost barriers to specialty drug use under Medicare Part D: addressing the problem of "too much too soon". *Am J Manag Care*. 2017;23(3 suppl):S39–S45.
33. Doshi JA, Pettit AR, Li P. Addressing out-of-pocket specialty drug costs in Medicare Part D: the good, the bad, the ugly, and the ignored. https://www.healthaffairs.org/do/10.1377/hblog20180724.734269/full/. Accessed January 18, 2019.
34. Lonergan R, Kinsella K, Duggan M, Jordan S, Hutchinson M, Tubridy N. Discontinuing disease-modifying therapy in progressive multiple sclerosis: can we stop what we have started? *Mult Scler*. 2009;15(12):1528–1531.
35. Burks J, Marshall TS, Ye X. Adherence to disease-modifying therapies and its impact on relapse, health resource utilization, and costs among patients with multiple sclerosis. *Clinicoecon Outcomes Res*. 2017;9:251–260.
36. Yermakov S, Davis M, Calnan M, et al. Impact of increasing adherence to disease-modifying therapies on healthcare resource utilization and direct medical and indirect work loss costs for patients with multiple sclerosis. *J Med Econ*. 2015;18(9):711–720.