Association between multiple sclerosis disease severity and adherence to disease-modifying therapies

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What is already known about this subject

- Multiple sclerosis (MS) is a chronic autoimmune disorder leading to demyelination of neurons throughout the central nervous system.
- Disease modifying therapies (DMTs) can delay disease progression, but barriers to DMT adherence such as perceived lack of efficacy, issues with injections, and adverse events can lead to poor adherence and increased cost burden to patients and plan sponsors.
- Although limited evidence is available, demographic parameters such as age, sex, DMT type, and comorbidities are associated with adherence rates.

What this study adds

- This retrospective study evaluated adherence to DMTs for the treatment of MS specific to the Medicare population.
- Disease severity is rarely considered when evaluating risk factors for poor adherence; however, patients with a high MS disease severity score were 53% less likely to be adherent compared to those patients with a low MS disease severity score.
- MS disease severity should be considered when evaluating risk of low adherence.

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ABSTRACT

BACKGROUND: For multiple sclerosis (MS) patients taking disease-modifying therapies (DMTs), adherence to treatment is a key component of achieving beneficial outcomes, such as delayed disease progression and the reduction and prevention of symptoms and relapses.

OBJECTIVES: The aim of this study was to assess the impact of a claims-based measure of MS disease severity on DMT adherence in a one-year study period.

METHODS: Patients were identified from Humana Medicare Advantage claims data from January 1, 2013 to December 31, 2015. Patients over the age of 18 with at least

12 months of continuous enrollment and >1 outpatient MS visit with DMT use prior to the index date were included. Patients who switched DMT type (oral, platform, IV) during the study period were excluded. Medication possession ratios (MPR) for DMTs were calculated from pharmacy and medical claims over 12 months of claims data, and a previously developed claims algorithm was used to determine MS disease severity. Patients with MPRs of 0.8 or higher were considered adherent to DMT treatment. Multivariable logistic regression was used to evaluate the association of MS disease severity, gender, DMT type, and age category with DMT adherence.

RESULTS: The study population of 3,347 patients had an average MPR of 84.7 (75%

were classified as adherent). Multivariable logistic analysis demonstrated that compared to the 18-45 age group, the 46-64 and 65+ age groups were 1.33 (OR: 1.33 [95% CI 1.08-1.64]) and 1.55 (OR: 1.55, [95% CI 1.18-2.05]) times more likely to be adherent. Patients with a high level of MS disease severity were 53% (OR: 0.47, [95% CI 0.36-0.62]) less likely to be adherent compared to those with low MS disease severity. No significant difference was identified for gender or DMT type (oral, platform, or IV).

CONCLUSIONS: Increased age and lower MS disease severity were associated with better DMT adherence. MS disease severity should be considered when assessing risk for low DMT adherence.

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) resulting in the demyelination of neurons throughout the brain and spinal cord.¹ Although no cure for MS exists, disease modifying therapies (DMTs) are often used to delay disease progression and reduce or prevent MS symptoms.²⁻⁵ As with many chronic diseases, management of MS is complicated by patient levels of DMT adherence.⁶ Poor adherence negatively impacts effectiveness of DMTs and increases cost burden on health plans, plan sponsors, and the healthcare system.⁷⁻¹¹ While there are many barriers to DMT adherence in MS patients, issues with injections, perceived lack of effectiveness, and adverse events have been identified as the most common.¹²

The fear of needles, anxiety, and dependence on another party to administer the medication are commonly cited problems of injections. A study published in 2001 showed that 10 out of 12 patients who missed at least one injection relied on another party to administer the injection.¹³ Other barriers to adherence can include forgetfulness and pill burden for oral agents and interference with daily activities for intravenous agents.^{14,15} In addition to these concerns, patients may perceive their treatment as unbeneficial. Many MS patients have intermittent symptoms and may not attribute their wellness to the treatment, thus failing to acknowledge the benefits of treatment. Alternatively, if symptoms begin to manifest in the patient, they may also believe the medication is failing. Unrealistic treatment expectations are a key factor of nonadherence in patients with chronic diseases.¹² Side effects can also contribute to a patient's decision to discontinue therapy. Many medications used to treat MS may produce adverse events such as flu-like symptoms, depression, injection site reactions, flushing, diarrhea, or headaches. These side effects may become intolerable, decreasing a patient's compliance to the medication regimen. Other factors influencing adherence can include, but are not limited to, treatment fatigue, cognitive deficits, and cost of treatment.¹²

DMTs are expensive and comprise about 65% of MS treatment costs.¹⁶ Thus, clinicians, payers, and caregivers have a vested interest in identifying factors associated with adherence. Literature assessing MS disease severity and its association with DMT adherence is limited. Early studies evaluating barriers to adherence or predictors of nonadherence identified factors such as a progressive course of MS, higher disability, lower self-efficacy, lower motivation to change, and lower perceived benefits as contributors to nonadherence.^{17,18} In 2016, a study explored the impact of age, sex, health plan, type of DMT, and history of depression on adherence.¹⁹ Age, sex, DMT type, and depression diagnosis were determined to have a statistically significant difference in adherence to DMTs. However, none of these

studies considered MS disease severity in their analysis. Other studies exploring adherence to oral DMTs did account for MS disease severity; however, the association between MS disease severity and adherence was not evaluated.^{20,21} To the best of our knowledge, few studies, if any, exist that explore the relationship between MS disease severity and DMT adherence. Although increasing adherence to DMTs is associated with better clinical outcomes, such as fewer MS comorbidities, relapses, hospitalizations and healthcare utilization, the factor driving this relationship has not been identified and cannot be assumed.^{22,23}

This study explored the association of various clinical and demographic variables on DMT adherence and provides insight into the adherence of a specific population (Medicare).

Methods

DATA SOURCE AND PATIENT POPULATION

This retrospective database study used Humana Medicare Advantage claims from January 1, 2013 to December 31, 2015. The Humana dataset includes Medicare claims for both medical (inpatient and outpatient) services and prescriptions.

Medicare patients over the age of 18 with 12 months of continuous enrollment and who met the definition of MS status were included in this study. MS status was defined as at least one MS outpatient claim (ICD-9: 340, ICD-10: G35) and at least one claim for a disease modifying therapy (DMT) no more than 180 days prior to the index date. The index date was defined such that the most recent 12 months of data were used. The study period refers to the 12 months following the index date. Patients who did not use a DMT or switched DMT types during the study period were excluded from the study. After all other exclusions, removing patients that switched DMT types during the study period reduced the study population by 258, or 7.2% (Figure 1). Patients that switched DMTs within a DMT type classification (eg, interferon beta-1a to glatiramer acetate) were not excluded by this criterion.

MS relapse was defined as an inpatient claim (hospitalization) with a listed principal diagnosis of MS or a claim for an outpatient visit with a listed diagnosis of MS in combination with intravenous or oral steroid use within 7 days. If multiple claims were present within a 30-day window, this was treated as a single relapse event, and the first available service date within such a grouping was deemed to be the relapse date.²⁴

FIGURE 1 Flow Chart for Study Inclusion

MS = multiple sclerosis, DMT = Disease-Modifying Therapy.

MULTIPLE SCLEROSIS DISEASE SEVERITY

MS disease severity in this study was derived from an algorithm that utilized summed weighted predictors in the study period.²⁵⁻²⁷ The algorithm used the binary presences of MS symptoms, disease modifying therapy (DMT) utilization, durable medical equipment (DME) utilization, MS-related hospitalizations, and MS relapses as MS disease severity predictors. DME included canes, walkers, wheelchairs, and hospital beds. A full list of MS symptoms, DME equipment, and the affiliated ICD-9, ICD-10, and CPT codes present in the database studied are available ([Supplementary Table 1](#) and [Supplementary Table 2](#), available in online article.) Based on the previously developed algorithm, MS disease severity predictors present in the baseline period were assigned the following weights: MS relapses or MS-related hospitalization and intravenous (IV) DMT use (natalizumab; weight = 3); cerebellar movement, cerebellar walking problems, bladder/bowel symptoms, and pyramidal symptoms (weight = 2); and eye symptoms, brainstem symptoms, speech symptoms, sensory symptoms, cognitive impairment, fatigue,

DME use, oral DMT use (dimethyl fumarate, fingolimod, teriflunomide), and platform DMT use (interferon beta-1a, peginterferon beta-1a, interferon beta-1b, glatiramer acetate; weight = 1). For example, patients with multiple relapses received the same weight of 3 as a patient with a singular relapse. The sum of the assigned weights for each patient provided an MS disease severity score. MS disease severity scores were divided into low (score 0-4), moderate (5-10) and high (≥ 11) severity categories. Although the algorithm has not been validated using the Expanded Disability Status Scale (EDSS), it has been shown to be strongly correlated with total healthcare cost and effective in estimating risk of relapse and MS-related hospitalizations.²⁵⁻²⁷ Thus, there is a reasonable expectation of accuracy.

MULTIPLE SCLEROSIS ADHERENCE

The primary outcome of interest was adherence to any DMT. Adherence to DMT was assessed using medication possession ratio (MPR) calculations. Adherence was measured during the year long (365 days) study period, and the

TABLE 1 Disease-Modifying Therapies (DMTs)

Type	Generic name	Brand name	Dosing	Days' supply (per dose)
Platform	interferon beta-1a	Avonex	Once weekly	7
	interferon beta-1a	Rebif	Thrice weekly	2
	peginterferon beta-1a	Plegridy	Every two weeks	14
	interferon beta-1b	Betaseron	Every other day	2
	glatiramer acetate	Copaxone	20 mg: once daily	1
			40 mg: thrice weekly	2
Oral	fingolimod	Gilenya	Once daily	1
	teriflunomide	Aubagio	Once daily	1
	dimethyl fumarate	Tecfidera	Once daily	1
Intravenous (IV)	natalizumab	Tysabri	Every four weeks	28

sum of days' supply was calculated by adding all the days' supplies from both prescription and medical claims provided through the year. This total number of days of therapy was then divided by 365 days in order to calculate each patient's MPR. MPR was capped at 1.0 for those with over 365 days of medication filled. Days' supply was provided for all DMT prescription claims since "days' supply" was a variable populated in the prescription files. However, for DMT utilization noted in medical claims, "days' supply" was assumed to be consistent with the Food and Drug Administration's package insert on MS dosing. In cases where dosing windows were provided, the most conservative days' supply was used. For example, a medication dosed 3 times weekly was assigned as providing 2 days' supply per dose, or 6 days' per week. Adherence was measured both as an average MPR and in a binary capacity based on a threshold MPR of greater than or equal to 80%. A sensitivity analysis was performed for MPR thresholds of greater than or equal to 70% and 90%.

TYPE OF DMT

This study examined adherence to different types of DMTs. Eight different DMTs were identified and categorized into three groups: platform (interferon beta-1a, interferon beta-1b, peginterferon beta-1a, glatiramer acetate), oral (dimethyl fumarate, fingolimod, teriflunomide), and IV (natalizumab). Table 1 summarizes the categorization of DMTs, dosing, and days' supply.

STATISTICAL TESTS

Comparisons of a binary measure of adherence (adherent vs non-adherent) for patients were compared for age category (Mann-Whitney U), gender (chi-square), DMT type (chi-square), and MS disease severity (Mann-Whitney U). Mann-Whitney U was considered appropriate to compare two independent groups of nominal (adherent vs non-adherent) and ordinal (low, moderate, high) data. In addition, a binary measure of adherence for patients was used to calculate the odds ratio for these various predictors using logistic regression. A sensitivity analysis for collinearity between DMT type and MS disease severity was performed by executing

the multivariable logistic regression with and without DMT type as a variable. An a priori level of $P < 0.05$ was used to determine statistical significance. The total number of tests performed was deemed low enough such that no correction was applied for multiple testing.

Results

Data from 3,347 patients were identified and included in the analysis (Figure 1). Demographic and clinical baseline characteristics for eligible MS patients are shown in Table 2. Of those included in the study, 65.6% and 17.2% were in the age categories of 46-64 and >65, respectively. Participants were primarily female (77.4%), white (78.7%), and geographically located in the American South (61.4%).

During the study period, 31.5%, 58.9%, and 9.6% used oral, platform, and IV DMTs, respectively. In the study population during the study period, 7.6% of patients experienced at least one MS-related hospitalization and 20.0% experienced at least one MS relapse.

The most prevalent baseline MS-related symptoms were fatigue (36.3%) and cerebellar walking problems (32.8%), followed by bladder symptoms (25.7%), pyramidal symptoms (21.5%), cerebellar movement problems (18.6%), brainstem symptoms (18.3%), sensory symptoms (14.7%), cerebral cognitive symptoms (12.2%), and eye symptoms (9.4%; See Table 2). In addition, 8.7% of the sample used durable medical equipment.

Table 3 outlines the MPR and adherence for each category investigated. The study population had an average MPR of 84.7 with 75% being adherent. Significant differences were detected between groups for MS disease severity ($P < 0.001$) and age category ($P < 0.001$). The percentage of adherent patients was 77%, 75%,

TABLE 2 Baseline Demographics, Utilization, and Disease Severity

Overall (N=3,347)	Mean	Standard deviation			Number of patients	Percentage (%)
Medication possession ratio (MPR)	0.85					
Percent adherence (MPR>0.8), %	75					
Age (years)	54.9	9.7				
	Number of patients	Percentage (%)				
Multiple sclerosis disease severity						
Low (0-4)					1,868	55.8
Moderate (5-10)					1,212	36.2
High (≥11)					267	8.0
DMT type during study period						
Oral					1,055	31.5
Platform					1,971	58.9
IV					321	9.6
Acute exacerbations during baseline						
>1 Hospitalizations					254	7.6
>1 Relapses					671	20.0
Symptoms experienced during baseline						
Eye					314	9.4
Brainstem					612	18.3
Cerebellar – walking					1,097	32.8
Cerebellar – movement					623	18.6
Pyramidal					720	21.5
Sensory					493	14.7
Bladder					861	25.7
Cerebral cognitive					410	12.2
Fatigue					1,215	36.3
Durable medical equipment use					291	8.7

DMT=Disease Modifying Therapy; IQR=interquartile range; MPR=medication possession ratio.

and 61% for low, moderate, and high MS disease severity, respectively. Analysis of adherence by age category demonstrated the highest percentage adherence in patients 65 or older (79%). The age category with the lowest percentage adherent was 18-45 (70%) with 46-64 in between (76%). No difference was seen in adherence levels between genders ($P=0.948$) or DMT type ($P=0.273$). The sensitivity analysis for MPR threshold demonstrated minimal fluctuation and did not impact results.

Multivariable logistic analysis demonstrated that the 46-64 and >65 age groups were 1.33 (OR: 1.33 [95% CI 1.08-1.64]) and 1.55 (OR: 1.55, [95% CI 1.18-2.05]) times more likely to be adherent compared to the 18-45 age group. Those with high MS disease severity were less likely to be adherent than their low MS disease severity counterparts (OR: 0.47, [95% CI 0.36-0.62]). Finally, those with moderate MS disease severity were 10% less likely to be adherent

compared to those with low MS disease severity although this difference was not statistically significant. Results of the multivariable logistic analysis are summarized in Table 4. The analysis was performed with MPR thresholds of 70%, 80%, and 90%, as well as with and without DMT type as a variable. The results were not sensitive to MPR threshold or collinearity between DMT type and MS disease severity.

Discussion

To the best of our knowledge, this study is one of the first to explore the relationship between MS disease severity and DMT adherence. Given the large proportion of US patients with MS enrolled in Medicare (25-30%),²⁸⁻³⁰ this study provides valuable insight into this population. The average age was similar to those identified in previous studies, as was

TABLE 3 MPR and Adherence by Variable

Variable	Average MPR (%)	Count	Adherent	Adherent Proportion	P Value
Multiple sclerosis disease severity					
Low	86.0	1,868	1,447	0.77	<0.001 ^b
Moderate	84.1	1,212	911	0.75	
High	77.8	267	163	0.61	
Gender					
Male	85.3	757	569	0.75	0.948 ^a
Female	84.5	2,590	1,952	0.75	
Disease-modifying therapy type					
Oral	83.8	2,055	797	0.76	0.273 ^a
Platform	85.4	1,971	1,494	0.76	
Intravenous (IV)	83.3	321	230	0.72	
Age category					
18-45	81.8	576	402	0.70	<0.001 ^b
46-64	85.1	2,196	1,667	0.76	
≥65	85.9	575	452	0.79	

^aChi squared.^bMann-Whitney U.

MPR=medication possession ratio.

the proportion of the population identifying as female.^{19,31} A recent study in 2020 demonstrated similar racial demographics.³¹ Of potential significance is the difference in number of relapses. Whereas we report 20% having >1 relapse, the aforementioned study reported a slightly higher value of 26%.³¹ This may be explained by regional differences in the sample population. With more than 60% of our participants identified as living in the South, relapses may be lower given the association between latitude and MS incidence.^{19,31-34} Another variable that could contribute to this difference is the type of MS, such as relapsing-remitting, primary progressive, and secondary progressive MS, although MS type was not captured in the claims data.

Our results indicated a higher average MPR and rate of adherence than

would typically be expected in the general population. We expect this difference is related to the population studied, Medicare patients, which agrees with comparisons between studies specific to commercial plans and those including Medicare patients.^{19,35} Medication adherence is a large component of Medicare Star Ratings and provides one possible explanation for the higher overall adherence rates generally seen in Medicare plans. Additionally, about 83% of our population was less than 65 years of age. It is reasonable to assume the majority of MS patients under the age of 65 on Medicare were enrolled due to disability since the only criteria for Medicare eligibility under age 65 is end-stage renal disease, amyotrophic lateral sclerosis, or at least 24 months of enrollment in Social Security Disability benefits. A

previous study demonstrated an association between disability and higher adherence which might explain the higher average MPR and rate of adherence found in our results.³¹

Statistical analyses demonstrated similar findings in multiple studies regarding adherence and age, with higher adherence being associated with increased age.^{19,36,37} This may be related to increased awareness of health status with older age,³⁸ however, the association between older age and adherence is not well understood.³⁷ Sex was not determined to be associated with adherence. Review of the literature indicates inconclusive findings regarding sex, with some reporting an association between men and increased adherence, albeit a relatively small increase.^{7,19,39}

DMT type was not associated with significant differences in adherence, although the trends appear to indicate better adherence with platform and oral DMTs. This agrees with other literature which also determined DMT type was not a statistically significant predictor of adherence; however, the studies referenced were not specific to Medicare patients.^{19,40} In contrast, some studies have shown the oral DMT fingolimod is associated with better adherence compared to injectable DMTs.^{21,41-43} Compared to IV and platform DMTs, oral DMTs benefit from convenient dosing intervals (once daily or twice daily) and does not involve needles. More research is needed to further evaluate the impact of newer oral DMTs and adherence.

The results indicate a significant difference in adherence exists between those with low MS disease severity and high MS disease severity. In other words, the severity of MS is associated with adherence. While patient factors (such as age, race, ethnicity, and sex) and medication factors (such as dosage form, route of administration, and side effects) are frequently considered

TABLE 4 Multivariable Logistic Analysis Results

Variable	Odds Ratio	95% Confidence Interval	P Value
Multiple sclerosis disease severity			
Low		Reference	
Moderate	0.90	0.76-1.07	0.236
High	0.47	0.36-0.62	<0.001
Gender			
Male		Reference	
Female	0.98	0.81-1.18	0.806
Disease-modifying therapy type			
Oral		Reference	
Platform	0.93	0.78-1.11	0.417
Intravenous (IV)	0.90	0.68-1.21	0.486
Age category			
18-45		Reference	
46-64	1.33	1.08-1.64	0.007
>65	1.55	1.18-2.05	0.002

when assessing risk of low adherence, the impact of disease severity is often neglected. Our study found that patients with a high MS disease severity score were 53% less likely to be adherent compared to the low MS disease severity group. Additionally, only 61% of patients in the high MS disease severity category met the criteria for adherence. This falls closer to average adherence rates for more common chronic disease states like hypercholesterolemia, osteoporosis, and type 2 diabetes.⁴⁴ This study indicates that MS disease severity is another important consideration when evaluating risk of low adherence.

While clinicians benefit from in-person patient visits and access to electronic health records to assess individual adherence risk factors, other decision makers are limited to claims data alone. This presents a challenge to various managed care plans seeking targeted interventions to improve health outcomes and mitigate costs at the population level. This study identifies a factor not yet considered in claims-based algorithms to identify MS patients at high risk of low adherence. By identifying discrete factors associated with low adherence that are accessible using claims data, decision makers can use those factors to tailor their adherence optimization strategies. For example, an MS disease severity score of >11 could be considered alongside factors such as age to identify which plan members would benefit from targeted calls and mail campaigns designed to improve adherence.

LIMITATIONS

The study is subject to limitations common to retrospective claims-based studies. These data do not differentiate between categories of MS such as relapsing-remitting MS or primary-progressive MS, which impact both drug selection and MS disease severity. This study does not include more recently approved MS DMTs such as cladribine (Mavenclad), ocrelizumab (Ocrevus), and ozanimod (Zeposia). This may decrease generalizability of results to present day. Additionally, claims-based adherence using MPR is an indirect measurement and cannot confirm actual medication use. Despite this limitation, claims-based adherence is commonly seen in the literature as a proxy for adherence.^{19,31}

This study may not translate to commercially insured patients as adherence is generally lower in these populations. Although studies demonstrate consistency in some relationships between adherence and factors like age and DMT type when comparing Medicare and commercial populations, this cannot be assumed for adherence and MS disease severity. We also recognize that 258 patients were excluded from this study for switching DMT types during the study period. This may further limit generalizability although only 7.2% of the population was removed by this exclusion. This was also performed to specifically examine patients assumed to be stable on therapy.

In addition, the days' supply for DMTs in medical files had to be estimated. Although these values were based on FDA dosing guidelines, package inserts, and previous studies with the most conservative ones being used in the final analysis, underestimation of days' supply is possible.

Finally, this study looked at the association between MS disease severity and adherence, not causation. Other variables, such as length of time with MS and previous treatment patterns were not included in the database. These variables may have been associated with treatment resistance to new therapies, which in turn might decrease adherence rates.

Conclusions

Adherence to DMTs in MS is associated with increased age and low MS disease severity. MS disease severity should be considered when evaluating risk of low adherence, in addition to patient and medication factors. Further analysis is warranted to consider newer agents, side-effect profiles of medications, and past treatment patterns. Future research should also be directed toward measuring the effects of targeted interventions in those populations demonstrating the lowest adherence rates.

DISCLOSURES

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