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Static and group-based trajectory analyses of factors associated with non-adherence in patients with multiple sclerosis newly-initiating once- or twice-daily oral disease-modifying therapy

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Abstract

Background: Increased understanding of adherence may facilitate optimal targeting of interventions.

Objective: To utilize group-based trajectory modeling (GBTM) to understand longitudinal patterns of adherence and factors associated with non-adherence in patients with multiple sclerosis (MS) newly-initiating once-/twice-daily oral disease-modifying therapy (DMT) (fingolimod, dimethyl fumarate, or teriflunomide).

Methods: Commercial plan data were analyzed using proportion of days covered (PDC) to evaluate factors associated with non-adherence. GBTM clustered patient subgroups with similar longitudinal patterns of adherence measured by monthly PDC (≥80%) and multinomial logistic regression identified factors associated with adherence trajectory subgroups.

Results: Among 7689 patients, 39.5% were non-adherent to once-/twice-daily oral DMTs. Characteristics associated with non-adherence (PDC<80%) included younger age, female, depression or migraine, switching during follow-up, more frequent dosing, relapse, and absence of magnetic resonance imaging. GBTM elucidated three adherence subgroups: Immediately Non-Adherent (14.9%); Gradually Non-Adherent (19.5%), and Adherent (65.6%). Additional factors associated with adherence (i.e. region, chronic lung disease) were identified and factors differed among trajectory subgroups.

Conclusion: These analyses confirmed that a significant proportion of patients with MS are non-adherent to once-/twice-daily oral DMTs. Unique patterns of non-adherence and factors associated with patterns of adherence emerged. The approach demonstrated how quantitative trajectories can help clinicians develop tailored interventions.

Keywords: Multiple sclerosis, non-adherence, disease-modifying therapy, newly-initiating, oral treatment, group-based trajectory modeling

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Introduction

Although disease-modifying therapy (DMT) has been shown to be effective in reducing relapse frequency and slowing disease progression in patients with multiple sclerosis (MS),[1,2] many patients with MS experience difficulties adhering to their treatment regimen.[3] A recently published meta-analysis of real-world adherence to oral DMT highlighted the evidence gap of this important component of effective patient care.[4] A better understanding of the adherence to prescribed DMT regimens is an important aspect of optimizing patient care in MS as it could help patients gain the full benefit from their treatment. Improvements in DMT adherence in patients with MS have the potential to reduce patient and payer burden in terms of improved clinical outcomes and

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lower medical resource utilization.[5–8] Adherence to treatment has been shown to be associated with a decreased risk of relapse, fewer severe relapses, emergency room (ER) visits, hospitalizations, and neuropsychological issues, lower costs, and increased quality of life.[5–12]

Encouraging adherence in MS is a complex issue as the disease course is unpredictable and a patient's viewpoints and medication adherence patterns may change as the disease progresses.[13] Patients' medication adherence patterns may vary over time and may require different clinical interventions and timing of interventions. Data on adherence can help inform treatment decisions for patients initiating therapy and those needing to switch treatment. Medication adherence studies typically use static measures of patient adherence: patient outcomes are defined based on the measure of adherence (e.g. proportion of days covered [PDC]) derived at the end of the time period of interest. However, such static measures of adherence do not provide information about the longitudinal course of adherence to treatment over time. In practice, patients with the same aggregate PDC adherence may exhibit very different patterns of adherence over time.

Group-based trajectory modeling (GBTM) may be used as an alternative approach for assessing adherence that overcomes the limitations of using a static adherence measure. Using GBTM, patients who experience or follow statistically similar longitudinal patterns of the outcome of interest are identified and "clustered" together.[14] GBTM can provide more detailed and dynamic longitudinal adherence pattern information, including graphical representations that may facilitate identification and targeting of patient subgroups for adherence-related interventions. Furthermore, by using GBTM to separate patients into different subgroups, the factors associated with adherence that may have been confounded when examining the entire population as a whole can be better elucidated.

The objective of this study was to use both static measures of adherence and trajectory modeling (GBTM) to better understand patterns of adherence and the factors associated with adherence in patients with MS newly-initiating once- or twice-daily oral DMTs (fingolimod, dimethyl fumarate, or teriflunomide). A longitudinal analysis of adherence was conducted consisting of: (1) identifying clusters of patients with MS who have similar patterns of adherence to once- or twice-daily oral DMTs over time; (2) characterizing the unique trajectories of adherence over time for the patient clusters; and (3) identifying factors associated with membership in the different adherence trajectory subgroups and determining whether these factors differed from those identified through traditional static adherence analysis.

Methods

Data source

This study utilized data from the IQVIA™ Real-World Data Adjudicated Claims—US database, which includes commercial health plan data for >150 million unique participants since 2006. Data includes medical and pharmacy claims (derived from reimbursement information or the payment of bills for healthcare services and commodities) and are generally representative of the <65 years of age, commercially insured population in the US with respect to both age and sex. The IQVIA™ Real-World Data Adjudicated Claims—US database is anonymized and compliant with the Health Insurance Portability and Accountability Act of 1996; as such, no institutional review board approval is required.

Patients

Eligible patients were 18–64 years old with at least two medical claims with a diagnosis for MS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 340.xx and ICD-10-CM code G35) and at least one claim for a once- or twice-daily oral maintenance DMT (fingolimod, dimethyl fumarate, or teriflunomide) between 1 July 2013 and 31 December 2016 (date of first claim = index date). Patients were required to have continuous eligibility with commercial insurance for at least 12 months prior and for 12 months after the index date (the follow-up period). Patients with any once- or twice-daily oral maintenance DMT claims in the baseline period were excluded; however, patients who had self-injectable or infusion DMTs during the baseline period were included.

Patient baseline characteristics

Demographic characteristics included: age at index (continuous), age group (categorical), sex, and US census region. Clinical characteristics included: overall comorbidity (as measured by the Charlson comorbidity index [CCI]) and commonly reported comorbidities in patients with MS based on the published literature (i.e. hypertension, hyperlipidemia, depression, gastrointestinal disease, thyroid disease, anxiety, migraine, diabetes, chronic lung disease, arthritis [rheumatoid arthritis or osteoarthritis], and alcohol abuse).[15]

Analyses

Adherence was evaluated during the follow-up period using PDC as a continuous variable (measured as the total number of days with medication supply [total prescription days' supply] in the follow-up period, divided by the duration of the follow-up period [12 months]). Adherence calculations were restricted to ambulatory days (i.e. days when the patient was not hospitalized). Adherence to the DMT was defined as PDC ≥0.8. Patients with no valid "days of supply" values (i.e. missing or 0) on relevant prescriptions were excluded from analyses. For descriptive (i.e. unadjusted) analyses, categorical variables were summarized using frequencies and percentages, while continuous variables were summarized using means, standard deviations (SDs), and medians (interquartile ranges [IQRs]). Both static (logistic regression considering adherence vs non-adherence) and longitudinal analysis of adherence (multinomial logistic regression considering adherence trajectory groups, identified with GBTM) were used to evaluate patterns of patient medication-taking behavior.

Static adherence analysis. For the static adherence analysis, overall adherence was evaluated for the patients at the end of the 1-year follow-up. Logistic regression evaluated the factors associated with adherence (PDC ≥0.8) to index DMT, expressed as odds ratios (OR; 95% CI). The logistic regression model considered the following variables derived from the literature: age groups and age at index, sex, US census region, CCI score, presence of select comorbidities not covered with the CCI (hypertension, hyperlipidemia, depression, diabetes, gastrointestinal disease, thyroid disease, anxiety, migraine, chronic lung disease, arthritis, and alcohol abuse), presence of any comorbidities, the most common combinations of comorbidities, number of comorbidities, 90-day pre-index neurologist visit, 90-day pre-index magnetic resonance imaging (MRI) scan, 90-day pre-index relapse (MS-related hospitalization, MS-related ER visit, MS-related outpatient visit plus corticosteroid within 7 days), 90-day pre-index any relapse, baseline medical costs, switching during follow-up, and daily dose (once vs twice). Patients who switched from their initial oral DMT to another DMT during the follow-up period were retained in the analyses and the PDC adherence measure accounted for the proportion of time on their initial oral treatment. The SAS STEPWISE method included in the SAS LOGISTIC procedure was used to identify the "best" subset of factors associated with non-adherence by removing any statistically non-significant variables from the model. All variables were considered for inclusion in the model. The stepwise method is a modification of the forward-selection technique and differs in that variables already in the model do not necessarily remain. The *p*-value cut-off is 0.05 for both adding variables and removing variables. Collinearity was also checked by examining the variance inflation factor for all selected covariates.

Longitudinal adherence analysis. GBTM is an application of finite mixture modeling that uses trajectory groups as a statistical device for approximating unknown trajectories across population members.[14] GBTM identifies distinct subpopulations showing similar patterns in their symptoms or behaviors.[14] GBTMs have increasingly been used in clinical research to understand the etiology and developmental course of a number of different types of diseases.[14,16–23] They can also be used to assess the heterogeneity in patients' responses to clinical interventions.[14]

Using the GBTM approach, the current study identified and "clustered" together patients who followed similar longitudinal patterns of adherence (PDC over time).[14] GBTM predicted the trajectory of each group, the form of each trajectory, estimated the probability for each patient of group membership, and assigned them to the group for which they had the highest probability.[24] Different models with a varying number of groups and shapes were compared to find the model that best fit the data. PDC trajectories can be described in terms of their turning (inflection) points that describe their overall shape (polynomial order). The first-order or linear polynomial suggests a linearly decreasing or increasing trajectory. The second-order or quadratic polynomial suggests a trajectory with one turning (i.e. inflection) point. For example, levels can initially increase and decrease after a peak is reached. The third-order or cubic polynomial suggests a trajectory with two turning points (inflections), a maximum and minimum. The fourth-order or quartic polynomial suggests a trajectory with three turning points (inflections). Quadratic, cubic, and quartic polynomial models were considered as described in the Results section. Several goodness-of-fit and model adequacy indices were used to compare different models and to select the best one, taking into account potential overfitting, underfitting, and information loss. A more detailed description of the GBTM approach is available in Supplemental Appendix 2.

Patient demographics, clinical characteristics, and healthcare resource use were used to identify differences in patient populations across adherence

Table 1. Demographic and clinical characteristics of patients newly initiating once- or twice-daily oral DMTs.

N	7689
Age (years)	
Mean (SD)	45.2 (10.2)
Median	46
IQR	38–53
Age groups	
18–24	240 (3.1%)
25–34	1029 (13.4%)
35–44	2197 (28.6%)
45–54	2624 (34.1%)
55–65	1599 (20.8%)
Sex	
Female	5833 (75.9%)
Male	1856 (24.1%)
US census region	
Midwest	2266 (29.5%)
Northeast	1928 (25.1%)
South	2581 (33.6%)
West	914 (11.9%)
CCI score	
Mean (SD)	0.40 (0.90)
Median	0
IQR	0–0
CCI score distribution	
0	5951 (77.4%)
1	814 (10.6%)
2	679 (8.8%)
3+	245 (3.2%)
Comorbidities	
Hypertension	1875 (24.4%)
Hyperlipidemia	1835 (23.9%)
Depression	1486 (19.3%)
Gastrointestinal disorders	1363 (17.7%)
Thyroid disease	1283 (16.7%)
Anxiety	1217 (15.8%)
Migraine	973 (12.7%)
Diabetes	583 (7.6%)
Chronic lung disease	570 (7.4%)
Arthritis	565 (7.4%)
Alcohol abuse	74 (0.96%)
Switching	
Yes	789 (10.3%)
No	6900 (89.7%)
Daily dose for the first oral DMT	
Once	2739 (35.6%)
Twice	4950 (64.4%)
90-day pre-index MRI	
No	4393 (57.1%)
Yes	3296 (42.9%)
90-day pre-index neurologist visit	
No	6261 (81.4%)
Yes	1428 (18.6%)
90-day pre-index relapse (hospitalization)	
No	7396 (96.2%)
Yes	293 (3.8%)
90-day pre-index ER relapses	
No	7250 (94.3%)
Yes	439 (5.7%)
90-day pre-index relapse (outpatient visit plus corticosteroid within 7 days)	
No	6368 (82.8%)
Yes	1321 (17.2%)
90-day pre-index any relapse	
No	5899 (76.7%)
Yes	1790 (23.3%)
Presence of any comorbidities	
No	5254 (68.3%)
Yes	2435 (31.7%)
Most common combinations of comorbidities	
Thyroid disease (only)	300 (3.9%)
Hypertension (only)	281 (3.7%)
Hyperlipidemia (only)	271 (3.5%)
Depression (only)	268 (3.5%)
Migraine (only)	237 (3.1%)
Gastrointestinal disorders (only)	229 (3.0%)
Anxiety (only)	211 (2.7%)
Hypertension and hyperlipidemia	195 (2.5%)
Anxiety and depression	103 (1.3%)
Chronic lung disease (only)	101 (1.3%)
Hyperlipidemia and thyroid disease	90 (1.2%)
None	2435 (31.7%)
Others	2968 (38.6%)
Number of comorbidities	
0	2435 (31.7%)
1	2033 (26.4%)
2	1393 (18.1%)
3	922 (12.0%)

Table 1. Continued.

N	7689
4	509 (6.6%)
5+	397 (5.2%)
Baseline medical costs	
Mean (SD)	$11,201 (17,881)
Median	$6151
IQR	$2797–12,485

CCI: Charlson comorbidity index; DMT: disease-modifying therapy; IQR: interquartile range; SD: standard deviation.

trajectory groups using multinomial logistic regression. The same covariates were included in the longitudinal adherence analysis as were used in the static adherence model. We checked for collinearity and examined the variance inflation factor for all selected covariates. More specifics related to this analysis are in Supplemental Appendix 3.

Results

Patients

A total of 7811 patients met the eligibility criteria, of which 122 patients had missing data, leaving 7689 patients included in the analysis. Mean (SD) patient age was 45.2 (10.2) years; 75.9% of patients were female (Table 1). Mean (SD) CCI score at baseline was 0.40 (0.90), and 77.4% of patients had a CCI score of 0. Common comorbidities included hypertension (24.4%), hyperlipidemia (23.9%), depression (19.3%), gastrointestinal disorders (17.7%), thyroid disease (16.7%), and anxiety (15.8%).

Outcomes

Static adherence analysis. Mean (SD) PDC across the entire analyzed data set was 0.73 (0.28) and median (IQR) PDC was 0.87 (0.59–0.93). Using the common threshold definition for non-adherence (PDC <0.8), 3036 (39.5%) patients were non-adherent to once- or twice-daily oral DMTs (fingolimod, dimethyl fumarate, or teriflunomide) over 1 year. The distribution of patients across 1-year PDC adherence rates was 0–<0.2 (761 [9.9%]), 0.2–<0.4 (600 [7.8%]), 0.4–<0.6 (590 [7.7%]), 0.6–<0.8 (1085 [14.1%]), and 0.8–<1.0 (4653 [60.5%]).

Demographic characteristics associated with a lower likelihood of treatment adherence included younger age (18–24 vs 25–34, 35–44, 45–54, and 55–64 years), female sex, and diagnosis of arthritis, depression, or migraine (Table 2). Switching, more frequent dosing (twice- vs once-daily), 90-day pre-index relapse requiring an ER visit, and absence of 90-day pre-index MRI scan were also associated with lower likelihood of adherence. Collinearity was checked after stepwise selection; the variance inflation factor for all selected covariates was less than 1.05 (see Supplemental Appendix 2).

Longitudinal adherence analysis GBTM elucidated three distinct patient groups of adherence over time: Immediately Non-Adherent (PDC ≤0.2 by Month 3; 14.9%); Gradually Non-Adherent (PDC >0.2 by Month 3 but ≤0.4 by Month 7; 19.5%); and Adherent (PDC ≥0.8; 65.6%) (Figure 1).

Specific factors were identified that were associated with different levels of adherence (Table 3). Female sex was consistently associated with greater non-adherence across comparisons of the three patient groups (Immediately vs Gradually Non-Adherent, Immediately Non-Adherent vs Adherent, and Gradually Non-Adherent vs Adherent). Additional factors that were associated with membership in the Immediately or Gradually Non-Adherent groups versus the Adherent group included US census region, chronic lung disease, depression, twice- (vs. once-) daily dose, and switching medication.

Comparison of baseline characteristics between the Adherent and Non-Adherent groups demonstrated several differences in the variables that were significant for the longitudinal adherence analysis compared with the static PDC adherence analysis (Table 4). Variables that were significantly associated with non-adherence in both the longitudinal and static PDC adherence analyses included younger age, female sex, depression, migraine, presence of a 90-day pre-index relapse requiring an ER visit, absence of 90-day pre-index MRI scan, twice- (vs. once-) daily dosing, and switching medication. US census region and chronic lung disease were significant factors associated with adherence in the longitudinal analysis but not in the static PDC adherence analysis, while arthritis was significantly associated with adherence in the static PDC adherence analysis, but not in the longitudinal analysis.

Discussion

Effective identification of patients with poor adherence and assessment of specific barriers to adherence

Table 2. Logistic regression model evaluating the factors associated with static 1-year adherence in patients newly initiating once- or twice-daily oral DMTs.

Variable[a]		OR estimates		
		Point estimate	95% Wald confidence limits	
Switching	Yes vs No	**0.026**	**0.019**	**0.036**
Sex	Female vs Male	**0.832**	**0.738**	**0.938**
Daily-dose	Twice vs Once	**0.825**	**0.742**	**0.916**
US census region	Midwest vs West	1.108	0.932	1.318
US census region	Northeast vs West	1.007	0.844	1.202
US census region	South vs West	0.897	0.757	1.062
Age groups	18–24 vs 25–34	**0.578**	**0.429**	**0.778**
Age groups	18–24 vs 35–44	**0.521**	**0.393**	**0.692**
Age groups	18–24 vs 45–54	**0.489**	**0.369**	**0.647**
Age groups	18–24 vs 55–65	**0.411**	**0.307**	**0.550**
Arthritis	Yes vs No	**0.815**	**0.672**	**0.987**
Depression	Yes vs No	**0.791**	**0.697**	**0.898**
Migraine	Yes vs No	**0.833**	**0.716**	**0.968**
90-day pre-index MRI	Yes vs No	**1.219**	**1.100**	**1.350**
90-day pre-index ER relapse	Yes vs No	**0.666**	**0.539**	**0.822**

Bolded items were found to be statistically significantly associated with non-adherence.
DMT: disease-modifying therapy; ER: emergency room; MRI: magnetic resonance imaging; OR: odds ratio.
[a]A stepwise selection included any variables from the model that were statistically significant, and re-evaluates all of the variables already included in the model in order to keep only those that improved performance.

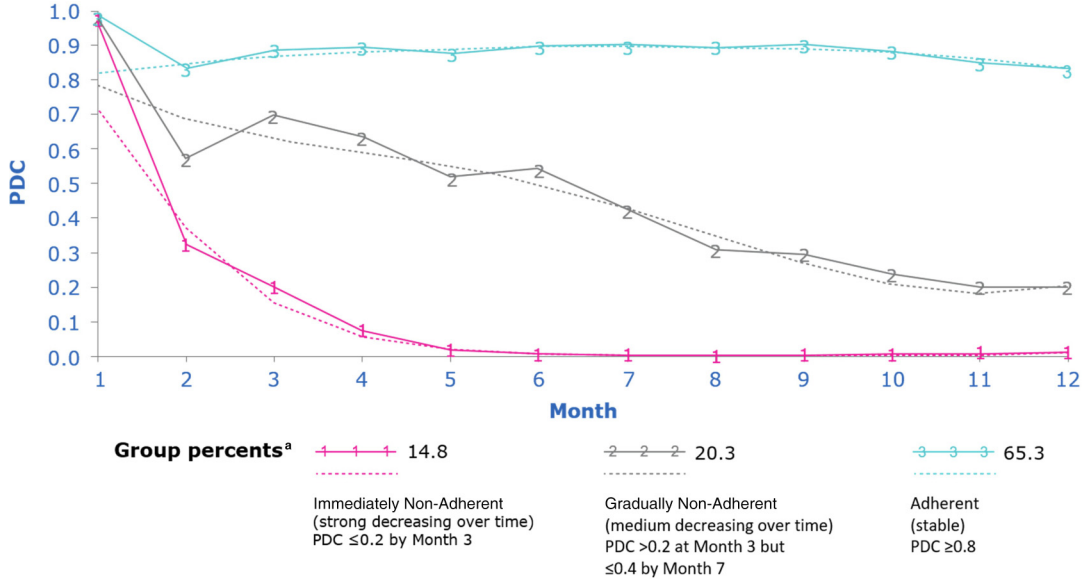

Figure 1. Adherence over time, 3 patient clusters (order of 4). [a]Estimated proportion of the sample belonging to a group, solid line = calculated mean percent; dotted line = estimated using GBTM. GBTM: group-based trajectory modeling; PDC: proportion of days covered.

Table 3. Factors associated with membership in the various adherence trajectory groups.

Parameter	Point estimate (95% Wald confidence limits)
Gradually Non-Adherent vs Immediately Non-Adherent	
Switching (Yes vs No)[b]	**0.252 (0.210, 0.304)**
Daily-dose (Twice vs Once per day)[b]	**0.767 (0.646, 0.912)**
Sex (Female vs Male)[a]	**0.809 (0.660, 0.991)**
US census region (Midwest vs West)	1.325 (0.992, 1.769)
US census region (Northwest vs West)[b]	**1.522 (1.134, 2.043)**
US census region (South vs West)	1.065 (0.804, 1.411)
Age[a]	**0.991 (0.983, 0.999)**
Chronic lung disease (Yes vs No)[a]	**0.740 (0.555, 0.986)**
Depression (Yes vs No)	0.994 (0.816, 1.211)
Migraine (Yes vs No)	0.940 (0.747, 1.183)
Baseline MRI (Yes vs No)	1.149 (0.974, 1.356)
Baseline ER relapse (Yes vs No)	0.929 (0.677, 1.275)
Adherent vs Immediately Non-Adherent	
Switching (Yes vs No)[b]	**0.020 (0.015, 0.026)**
Daily-dose (Twice vs Once per day)[b]	**0.746 (0.638, 0.874)**
Sex (Female vs Male)[b]	**0.684 (0.568, 0.823)**
US census region (Midwest vs West)	0.962 (0.745, 1.242)
US census region (Northwest vs West)	0.906 (0.697, 1.178)
US census region (South vs West)[a]	**0.773 (0.603, 0.990)**
Age	1.001 (0.994, 1.009)
Chronic lung disease (Yes vs No)[b]	**0.678 (0.525, 0.876)**
Depression (Yes vs No)[a]	**0.828 (0.691, 0.992)**
Migraine (Yes vs No)[a]	**0.796 (0.645, 0.984)**
90-day pre-index MRI (Yes vs No)[b]	**1.227 (1.055, 1.426)**
90-day pre-index ER relapse (Yes vs No)[a]	**0.699 (0.521, 0.938)**

Bolded values denote statistically significant differences vs. the reference group.
ER: emergency room; MRI: magnetic resonance imaging; Pr > ChiSq: probability of observing a Chi-square statistic greater than that of the null hypothesis.
[a]Pr > ChiSq < 0.05.
[b]Pr > ChiSq < 0.01.

in clinical settings may facilitate the targeting of appropriate interventions to specific patients at the correct point in their treatment pathway. Increased understanding of barriers to DMT adherence may help to inform appropriate initial selection of therapeutic agents for patients starting treatment, as well as for those who may need to switch treatment.[25]

Static measures of patient adherence offer limited correlation to real-world scenarios when considering the longitudinal course of adherence to treatment over time; despite having the same aggregate PDC adherence, patients may follow very different patterns of treatment adherence over the course of their disease. A longitudinal analysis, however, can provide more detailed and dynamic longitudinal adherence pattern information. Particularly, GBTM enables the identification of clusters or groups of patients with similar patterns of adherence and it can graphically depict the adherence trajectory for each of these groups. Multinomial logistic regression then enables evaluation of factors associated with adherence for the separate adherence trajectory groupings.

Static adherence analyses from this large-scale study showed that a substantial proportion (39.5%) of patients with MS newly initiating once- or twice-daily oral DMTs (fingolimod, dimethyl fumarate, or teriflunomide) were non-adherent at 1 year. Factors associated with static non-adherence included younger age, female sex, diagnosis of depression or migraine, switching, more frequent dosing (twice- vs once-daily), 90-day pre-index relapse requiring an ER visit, and absence of 90-day pre-index MRI scan.

Table 4. Comparison of baseline characteristics between adherent and non-adherent groups for GBTM and static PDC adherence analyses.

	Variable	Adherence groups based on GBTM	Static PDC adherence analysis
Treatment characteristics	Switching	✓	✓
	Daily dose (twice vs once per day)	✓	✓
Demographic characteristics	Age	✓	✓
	Sex	✓	✓
	US census region	✓	
Clinical characteristics	CCI score groups		
	Alcohol abuse		
	Anxiety		
	Arthritis		✓
	Chronic lung disease	✓	
	Depression	✓	✓
	Diabetes		
	Gastrointestinal disorders		
	Hyperlipidemia		
	Hypertension		
	Migraine	✓	✓
	Thyroid disease		
	Any comorbidities		
	Comorbidities types		
	Number of comorbidities		
	90-day pre-index relapse (Any reason)		
	90-day pre-index relapse (ER visits)	✓	✓
	90-day pre-index relapse (Hospitalization)		
	90-day pre-index relapse (Outpatient visits)		
Healthcare resource use (90 days pre-index)	MRI	✓	✓
	Neurology visits		
	Medical costs		

✓Significant differences between variables for both the GBTM and static adherence analyses.
✓Significant difference for either the GBTM or static adherence analysis.
CCI: Charlson comorbidity index; ER: emergency room; GBTM: group-based trajectory modeling; MRI: magnetic resonance imaging; PDC: proportion of days covered.

GBTM analysis elucidated three patterns of adherence: the "Immediately Non-Adherent" group (PDC ≤0.2 by Month 3) comprised 14.9% of patients studied, the "Gradually Non-Adherent" group (PDC >0.2 at Month 3 but ≤0.4 by Month 7) comprised 19.5% of patients and the "Adherent" group (PDC ≥0.8) comprised 65.6% of patients with MS in this study. There were differences in the factors associated with adherence among the groups in the longitudinal analysis. The identification of three groups that correspond to typical clinical perceptions of different patterns of patient adherence reinforces how the GBTM approach and the statistical goodness-of-fit indices can bring quantitative evaluation of clinicians' perspectives. Use of known factors in the literature to guide the variables considered and how their relevance differed across adherence groups demonstrated the value of digging deeper into how these variables combine differently in the three patient subgroups.

The longitudinal analysis reinforced the importance of the most significant factors associated with adherence identified in the static analyses and in the literature (i.e. switching, daily dose, age, gender, depression, migraine, relapse requiring an ER visit, and presence of an MRI scan in the 90 days prior to DMT initiation). However, the more delineated longitudinal analyses also uncovered US census region and chronic lung disease as statistically significantly associated with adherence. Arthritis, which was significant in the static analyses but not in the longitudinal analyses, may be a confounder. While we employed several goodness-of-fit and model adequacy indices to compare models and select the best one to avoid potential overfitting, underfitting, and information loss, we recognize that examination from the clinical point of view and with subsequent research is necessary before making inferences.

The linkage between adherence and the specific clinical comorbidities that were significant is unclear given the use of claims data for the analyses. The burden of multiple medications for multiple chronic diseases combined with depression may be a notable consideration for the "Immediately Non-Adherent group" as well as for the "Gradually Non-Adherent" group eventually. It is difficult to discern "why" and how these variables (along with frequency of dosing) are leading to non-adherence using claims data. The ability to cope with medication dosing regimens cannot be appropriately discerned without in-depth studies with patients directly. Subsequent investigations to gain insights into why subgroups of patients may be non-adherent could focus on the addition of electronic health record data which could provide insights into clinical measures such as tolerability and also social determinants of health related to access and outcomes. Ultimately, the goal of such research would be customized adherence interventions that specifically address the various contributors to non-adherence.

Previously published studies in patients with MS have utilized GBTM to assess MS disease course[26] and disability outcomes.[27] One previously published study compared adherence trajectories between fingolimod and self-injectable DMTs in patients with MS.[28] Similar to the current study, the authors found that GBTM grouped individuals in the study cohort into three adherence trajectories—complete adherers (49.9%), slow decliners (26.6%), and rapid discontinuers (23.5%).[28] A multinomial logistic regression model found that oral fingolimod users had higher odds of being a complete adherer (adjusted odds ratio [AOR]: 2.78, 95% CI: 1.85–4.16) or a slow discontinuer (AOR: 2.62, 95% CI: 1.70–4.05) compared with injectable DMT users.[28] The overall 1-year static DMT adherence rate observed in the current study is also consistent with other studies assessing oral DMT adherence, which have considered smaller populations receiving an oral DMT for treatment of MS.[5,15,29–32]

Adherence to DMTs is an important aspect of optimizing patient care in MS, as greater adherence has been shown to be associated with a decreased risk of relapse, fewer ER visits, hospitalizations, days of work lost, neuropsychological issues, costs, and an increased quality of life.[5–12] The most recent study by Burks and colleagues (2017) showed that, compared with non-adherence, adherence to DMTs over 1 year significantly reduced the likelihood of relapse by 42%, hospitalization by 52%, and ER visits by 38% (all $P < 0.0001$).[5] In addition to increased quality of life that may be associated with reduced relapse, patients adherent to their treatment regimen have on average 0.7 fewer outpatient visits annually, compared with non-adherent patients ($P < 0.0001$).[5]

Limitations of this study include that adherence to DMT was assessed based on dispensed medications. It is not known whether the patients actually took their medications. New initiation of once- or twice-daily oral DMT medication was defined as no evidence of oral DMT (fingolimod, dimethyl fumarate, or teriflunomide) use during the 1-year baseline period. It is possible that patients received fingolimod, dimethyl fumarate, or teriflunomide earlier than 1 year before study initiation. Additionally, the administrative claims data used in this study are largely derived from patients with commercial health insurance, and our data may not be generalizable to patients who do not have commercial health insurance. In terms of the modeling approach, only time-invariant or fixed characteristics were considered in the modeling with trajectory membership.

Another limitation of this analysis is that data available from administrative claims are limited. Claims data are collected for reimbursement purposes and not specifically for research, and the lack of clinical variables limit the inferences that can be made from the data. The ICD-9-CM and ICD-10-CM codes for MS do not distinguish between different types of MS, such as relapsing-remitting or primary progressive MS. Furthermore, other clinical aspects that may be important for adherence, such as codes related to tolerability, were not considered. Future evaluations may be enhanced with additional data if available.

In summary, many patients with MS did not adhere to once- or twice-daily oral maintenance DMTs (fingolimod, dimethyl fumarate, or teriflunomide). Enhanced methods to characterize patients with poor adherence and to assess specific barriers to adherence in clinical settings may facilitate the targeting of appropriate interventions to specific patients at the correct time. To our knowledge, this is the first study to explore differences in medication adherence trajectories in patients with MS. GBTM enabled the identification of clusters or groups of patients with similar patterns of adherence and enabled the graphical depiction of each cluster's trajectory of adherence over time.[16–23] Factors associated with adherence differed among the adherence trajectory groups and compared to the static adherence analysis, demonstrating the complexity of addressing DMT adherence among patients with MS. The approach demonstrated how quantitative evaluation can generate evidence aligned with clinician perceptions. These analyses suggest subsequent research with more variables that affect adherence is needed with the ultimate goal of more customized adherence interventions so that more patients with MS can achieve their treatment outcomes.

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Supplemental material

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