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Patient-Reported Disease-Modifying Therapy Adherence in the Clinic: A Reliable Metric?

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Abstract

Background: Adherence to multiple sclerosis (MS) disease-modifying therapy (DMT) is commonly assessed through patient reporting, but patient-reported adherence is rarely studied.

Objective: To determine rates of DMT adherence reported from patient to clinician, reasons for non-adherence, and relationships between adherence and outcomes.

Methods: We identified relapsing–remitting MS patients on DMT for $\geq$3 months. DMT adherence was defined as taking $\geq$80% of doses. Linear and logistic regression models were created used to determine the association of baseline adherence with several patient reported outcomes and the timed 25-foot walk at 6 months, 1 year, 2 years, and 3 years after the index visit.

Results: The analysis included 1148 patients, of whom 501 had data at 6 months, 544 at 1 year, 331 at 2 years, and 247 at 3 years. Baseline adherence was 94.9% and overall adherence was 93.1%. Forgetting was the most common reason for missed doses. In the adjusted models, adherence was not associated with the outcomes.

Conclusions: Higher than expected adherence and a lack of association between adherence and outcomes suggests patient reported adherence may not be reliable. Further research is needed to clarify the relationship between patient-reported adherence and relapses or new lesion formation.

Keywords: Multiple sclerosis, disease-modifying therapies

Introduction

Fourteen disease-modifying therapies (DMTs) are approved for treatment of multiple sclerosis (MS) in the USA. The wide range of therapies, some of which are highly effective, has led many neurologists to adopt a "treat to target" approach in which treatment efficacy is continually reassessed. A common recommendation is to change DMT when breakthrough disease activity occurs.[1] However, when considering treatment changes, it is important to know if patients have been adherent to the prescribed therapy.

A number of obstacles to DMT adherence exist, including medication side effects, needle fatigue, and irregular dosing schedules with some agents. Further, the significant expense of MS DMTs can lead to non-adherence during lapses in insurance coverage or while waiting for prior authorization.

Previous research into DMT adherence has focused on claims data and formal research questionnaires in an attempt to maximize the accuracy of adherence estimates and correlate them with relevant outcomes. Adherence has generally been estimated at 27–75% in such studies.[2,3] Unfortunately, claims data and research questionnaires are not routinely available in the clinic setting and most treatment decisions are made on the basis of patient self-reported adherence.

We investigated real world patient self-reported DMT adherence and its impact on both patient-reported outcomes (PRO) and the timed 25-foot

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walk (T25FW). We hypothesized that patients who were adherent to their DMT would have better PRO scores and less decline in their walking speed over time.

Methods

Patients

The Mellen Center is a tertiary MS referral and longitudinal care center at Cleveland Clinic, Cleveland, Ohio, USA. The Knowledge Program (KP) is a Cleveland Clinic initiative to collect patient and clinician reported outcomes electronically at each clinical encounter.[4] Collection began in 2007 and we have accumulated single visit or longitudinal data on more than 16,000 patients. Prior to each encounter, patients complete several validated questionnaires by computer and the results are automatically sent to the KP database. These include the Performance Scales (PS, a measure of MS-related disability),[5,6] the European Quality of Life 5 Dimensions (EQ5D, a measure of quality of life),[7] and the Patient Health Questionnaire 9 (PHQ9, a depression measure).[8] Clinicians later electronically record the T25FW, as well as the symptom onset date, date of diagnosis, MS phenotype, and current DMT.

After obtaining institutional review board approval, the KP was queried for patients with relapsing–remitting MS who were treated between 1 January 2011 and 31 December 2015. To be included in the study, patients had to be aged 18–70 years and had to be on a DMT for at least 3 months leading up to the index visit. Individuals over 70 years of age were excluded due to concern that concurrent comorbid conditions might significantly affect the outcomes of interest. Individuals with progressive forms of MS were excluded. The first visit after 1 January 2011 was the index visit. To be included in the analysis, the patients had to have at least one additional visit at 6 months (±3 months), 1 year (±3 months), 2 years (±6 months), or 3 years (±6 months).

Data Collection

Using the identified subjects, the electronic medical record (EMR) was reviewed to acquire adherence data. As part of the standardized Mellen Center follow-up visit template, the number of missed DMT doses, and the reason for any missed doses over the prior 3 months is asked of the patient or caregiver by the clinician and recorded. This information, as well as the reason for missed doses, was extracted from the EMR for each visit. Baseline adherence was calculated from the number of

doses missed at the first appointment after 1 January 2011. Adherence was also calculated at the 6-month, 1-year, 2-year, and 3-year time points for patients with the appropriate data. If the number of missed doses exceeded 20% of expected doses, the patient was considered non-adherent at that time point. A sensitivity analysis was also conducted in which any missed doses over the prior 3 months was considered nonadherence.

The EMR was also reviewed to determine the number of relapses in the year prior to the baseline visit. A prespecified definition was applied to standardize relapse determinations. To qualify as a relapse, the episode had to be specifically referred to as a relapse by the clinician, or it had to be described as an episode of worsening neurological disability treated with high dose corticosteroids.

Statistical Methods

To determine whether adherence was related to outcomes in this population, separate linear and logistic regression models were created for each time point. Each patient's index visit served as the baseline time point. Outcomes were evaluated at approximately 6 (±3), 12 (±3), 24 (±6), and 36 (±6) months post-baseline. Overall adherence was determined through a generalized estimating equation to account for repeated measures.

The primary outcome was the effect size of baseline adherence on PS scores at each time point. Secondary outcomes included the effect size of baseline adherence on EQ5D, PHQ9, and T25FW scores. We also analyzed the effect of time-specific adherence on the PS, EQ5D, PHQ9, and the T25FW by using the adherence level reported at the same visit during which the outcomes were assessed.

Both adjusted and unadjusted models were constructed. The adjusted models included the following covariates obtained at baseline: age, sex, race (white, black, other), marital status (married, single, divorced, widowed), payer (private, self-pay, Medicare, Medicaid), smoking status (current, former, never), median income by zip code, time since MS diagnosis, number of relapses in the year prior to the baseline visit, walking aid (unilateral, bilateral, none), disease modifying therapy (interferon beta, glatiramer acetate, natalizumab, fingolimod, other), PHQ-9 score (except in the model with PHQ-9 score as the dependent variable), and time since first outpatient visit in the study period. Further, we adjusted each model by the baseline score for the

outcome in question. As a sensitivity analysis, the same models were run a second time with adherence defined as missing zero doses over the prior 3 months.

The reasons given for missed doses were consolidated into six categories: forgetting, patient choice (e.g. tired/busy, dislikes taking the medication, poor mood), medication access problems (e.g. cost, insurance denials, no refills), social issues (e.g. stressors, travel, or no caregiver to help with administration), general health problems (e.g. abnormal labs, hospitalization, other illness), and medication side effects. If no reason for missed doses was indicated, the reason was classified as "unknown." Percentages for each reason were calculated based on reports of non-adherence across all visits.

Finally, outcomes were further validated by exploring their correlations at different time points. Pairwise Spearman correlation coefficients were computed between the PS, EQ5D, PHQ9, and T25FW at baseline, 6 months, 1 year, 2 years, and 3 years.

All analyses were conducted using R version 3.3.3 (https://cran.r-project.org/) and p values < 0.05 were considered statistically significant.

Missing Data
Multiple imputation was used to create and analyze 100 imputed datasets.[9] Incomplete variables were imputed under fully conditional specification using the default settings of the mice 2.13 package.[10,11] Model parameters were estimated with linear and logistic regression applied to each imputed dataset separately.

Results
A total of 1148 patients met criteria for the analysis. Of these, 501 had the requisite data for analysis at 6 months, 544 at 1 year, 331 at 2 years, and 247 at 3 years. Baseline cohort characteristics are summarized in Table 1. The average age was 45.8 years and the average disease duration was 8.1 years. Only 59 patients (5.1%) reported taking ≤80% of their DMT doses at the baseline visit. Interestingly, patients with longer disease duration were significantly more likely to be non-adherent. Adherence levels at 6 months, 1 year, 2 years, and 3 years were 95.2%, 93.9%, 91.8%, and 91.6% respectively. Overall adherence was estimated at 93.8%.

The effect of baseline adherence on outcomes at 6 months, 1 year, 2 years, and 3 years is reported in

Table 2. In the unadjusted model, patients who were adherent had significantly lower PS scores (less disability) at 2 years than non-adherent patients ($\beta = -1.65$, 95% confidence interval (CI) = −3.25 to −0.04, $p = 0.044$). There were trends towards lower PS scores among adherent patients at other time points, but none reached significance. In the adjusted models, adherent patients had lower PS scores at all times points, but the differences did not reach significance.

In the unadjusted model, adherent patients had slightly lower EQ5D scores (lower quality of life) at 1 year than non-adherent patients ($\beta = -0.05$, 95% CI = −0.098 to −0.002, $p = 0.043$). No other significant differences were seen with respect to EQ5D scores in either model.

Adherent patients trended towards lower PHQ-9 scores (less depression) in both models but the difference was not statistically significant. This result was highest at 2 years when the effect size was −1.26 (95% CI = −2.80 to 0.28) in the unadjusted model and −1.01 (95% CI = −2.60 to 0.58) in the adjusted model.

Variation in the T25FW between adherent and non-adherent patients was minimal at all time points in both the adjusted and unadjusted models. The largest difference was 0.23 s (favoring non-adherent patients), but none of the differences were significant.

Findings from the models based on time-specific adherence levels are presented in Table 3. In this analysis, adherent patients had lower PS scores in both the adjusted and unadjusted models. However, these results did not reach statistical significance. No consistent effect of adherence on the EQ5D, PHQ9, or T25FW was seen in either the adjusted or the unadjusted models of current adherence.

In the sensitivity analysis where adherence was defined as not missing any doses over the prior 3 months, there were 350 nonadherent patients at baseline (30.5%), 217 at 6 months (30.6%), 221 at 1 year (28.5%), 144 at 2 years (29.7%), and 102 at 3 years (30.5%). In the unadjusted model, patients who were adherent at baseline had significantly better PS, PHQ9, and EQ5D scores at 2 years (Supplementary Table 1). There was no significant difference in outcomes between adherent and non-adherent patients at the other time points. When time-specific, rather than baseline adherence, was used, adherent patients had significantly lower

Table 1. Cohort characteristics at the baseline visit.

	All Patients	Adherent	Not Adherent	*p*-Value
N	1148	1089	59	
Age, Mean (SD)	45.8 (10.3)	45.9 (10.3)	44.2 (10.5)	0.244
Female	841 (73.3%)	801 (73.6%)	40 (67.8%)	0.365
Race				
White	1017 (88.6%)	966 (88.7%)	51 (86.4%)	0.251
Black	109 (9.5%)	103 (9.5%)	6 (10.2%)	
Other	14 (1.2%)	12 (1.1%)	2 (3.4%)	
Missing/unknown	8 (0.7%)	8 (0.7%)	0 (0.0%)	
Marital Status				
Married	789 (68.7%)	751 (69.0%)	38 (64.4%)	0.307
Single	255 (22.2%)	239 (21.9%)	16 (27.1%)	
Divorced	66 (5.7%)	64 (5.9%)	2 (3.4%)	
Widowed	17 (1.5%)	15 (1.4%)	2 (3.4%)	
Missing/unknown	21 (1.8%)	20 (1.8%)	1 (1.7%)	
Insurance				
Private	674 (58.7%)	634 (58.2%)	40 (67.8%)	0.098
Self-pay	314 (27.4%)	304 (27.9%)	10 (16.9%)	
Medicaid	37 (3.2%)	33 (3.0%)	4 (6.8%)	
Medicare	112 (9.8%)	107 (9.8%)	5 (8.5%)	
Missing/unknown	11 (1.0%)	11 (1.0%)	0 (0.0%)	
Smoking Status				
Current	164 (14.3%)	153 (14.0%)	11 (18.6%)	0.218
Former	314 (27.4%)	296 (27.2%)	18 (30.5%)	
Never	583 (50.8%)	560 (51.4%)	23 (39.0%)	
Missing/unknown	87 (7.6%)	80 (7.3%)	7 (11.9%)	
Median Income (x US$1000), Mean (SD)	55.2 (17.5)	55.2 (17.5)	56.8 (17.6)	0.414
Years Since Diagnosis, Mean (SD)	8.1 (6.3)	8.0 (6.3)	9.9 (6.3)	0.016
Assisted Device				
Unilateral	47 (4.1%)	46 (4.2%)	1 (1.7%)	0.839
Bilateral	26 (2.3%)	25 (2.3%)	1 (1.7%)	
Non-ambulatory	2 (0.2%)	2 (0.2%)	0 (0.0%)	
None	745 (64.9%)	705 (64.7%)	40 (67.8%)	
Missing/unknown	328 (28.6%)	311 (28.6%)	17 (28.8%)	
Confirmed Relapses in the Prior Year	289 (25.2%)	274 (25.2%)	15 (25.4%)	1.000
PS Score, Median (IQR)	7 (4, 12)	7 (3, 12)	8 (4, 12)	0.416
T25FW Time (s), Median (IQR)	5.2 (4.5, 6.4)	5.2 (4.5, 6.4)	5.25 (4.6, 6.55)	0.512
EQ5D Index, Median (IQR)	0.83 (0.77, 1)	0.83 (0.77, 1)	0.815 (0.7675, 0.84)	0.090
PHQ-9 Score, Median (IQR)	3 (1, 7)	3 (1, 7)	4 (2, 6.25)	0.089

PS: performance scales; T25FW: timed 25-foot walk; EQ5D: European Quality of Life 5 Dimensions; PHQ-9: patient health questionnaire 9; IQR: interquartile range.

PHQ9 scores at 1 year, but no other significant differences were observed (Supplementary Table 2).

Patient-reported reasons for missed doses are shown in Table 4. Nearly one-third of missed doses were due to the patient forgetting to take their medication. The second most common reason for missed doses was a conscious patient decision not to take their DMT, for reasons such as feeling too tired or being too busy to take the medication. Almost 10% of missed doses were due to medication access problems such as waiting for prior authorization from insurers or running out of refills.

Table 5 shows the correlation coefficients between our outcomes at baseline, 6 months, 1 year, 2 years, and 3 years. Correlation scores were remarkably consistent across the study period. For instance, the

Table 2. Effect of baseline adherence on study outcomes.

	N	Not Adjusted for Covariates		Adjusted for Covariates	
		Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
PS					
6 months	501	−0.44 (−2.04, 1.16)	0.588	−0.72 (−2.35, 0.91)	0.386
1 year	544	−0.32 (−1.70, 1.07)	0.655	−0.41 (−1.83, 1.01)	0.572
2 years	331	−1.65 (−3.25, −0.04)	0.044*	−1.56 (−3.23, 0.11)	0.067
3 years	247	−1.53 (−4.38, 1.33)	0.293	−1.51 (−4.40, 1.37)	0.303
PHQ−9					
6 months	538	−0.54 (−2.00, 0.92)	0.465	−0.45 (−1.96, 1.07)	0.561
1 year	590	−0.12 (−1.41, 1.18)	0.860	−0.07 (−1.40, 1.26)	0.915
2 years	363	−1.26 (−2.80, 0.28)	0.107	−1.01 (−2.60, 0.58)	0.211
3 years	256	−0.63 (−3.20, 1.94)	0.632	−0.78 (−3.35, 1.79)	0.551
EQ5D					
6 months	567	0.040 (−0.015, 0.095)	0.155	0.030 (−0.026, 0.085)	0.296
1 year	623	−0.050 (−0.098, −0.002)	0.043*	−0.041 (−0.089, 0.007)	0.092
2 years	371	0.035 (−0.019, 0.089)	0.200	0.034 (−0.021, 0.089)	0.228
3 years	259	−0.018 (−0.111, 0.075)	0.701	−0.030 (−0.125, 0.065)	0.533
T25FW					
6 months	593	0.13 (−0.31, 0.57)	0.564	0.21 (−0.21, 0.64)	0.326
1 year	662	0.21 (−0.15, 0.58)	0.255	0.23 (−0.12, 0.58)	0.201
2 years	412	−0.06 (−0.45, 0.33)	0.772	0.03 (−0.36, 0.41)	0.893
3 years	297	−0.01 (−0.56, 0.54)	0.969	0.17 (−0.36, 0.69)	0.536

PS: Performance scales; PHQ-9: Patient Health Questionnaire 9; EQ5D: European Quality of Life 5 Dimensions; T25FW: Timed 25-foot walk; CI: confidence interval.

correlation coefficient for PS with T25FW (0.53–0.57), EQ5D (–0.80 to –0.75), and PHQ9 (0.64–0.75) showed minimal variance across the 3 years of follow-up.

The directions of the correlations were as expected. The strongest negative correlations were between PS and EQ5D (greater disability correlating with lower quality of life) and between EQ5D and PHQ9 (lower quality of life correlating with more depression). The strongest positive correlation was between PS and PHQ9 (higher disability correlating with more depression).

Discussion

Our study investigated patient reported adherence to injectable, oral, and intravenous DMTs in a real-world setting. We found that 93.8% of patients reported ≥80% adherence to their DMTs. We also sought to classify the association of patient reported adherence with the T25FW and several PROs over time. While there were trends suggesting adherent patients developed less disability, none of these assessments reached significance when adjusted for important covariates. To our knowledge, this is the only study of MS DMT adherence that has incorporated longitudinal patient report in the clinic as the metric for adherence assessment.

MS DMT adherence has been explored in several previous studies, although most were conducted before oral DMTs were available. The global adherence project was a cross-sectional study of 2648 patients in which adherence was assessed by questionnaires privately completed by participants.[3] Adherence was defined as zero missed doses over the prior 4 weeks and 75% of patients were adherent by this criterion. Steinberg et al. reported a study of 1606 patients receiving interferon β therapy.[2] Pharmacy and claims data were used to calculate a medication possession ratio, with patients who ordered >85% of the expected medication being considered adherent. Adherence rates ranged from 27% to 41% over the 3-year study and only 4% of patients were adherent for the entire 3 years. A more recent study of injectable medication use in Lithuania used patient questionnaires to assess adherence, which was defined as missing no doses over the prior 3 months.[12] Of the 207 patients enrolled, 64.7% were adherent.

Table 3. Effect of time-specific adherence on study outcomes.

	N	Not Adjusted for Covariates		Adjusted for Covariates	
		Estimate (95% CI)	p-alue	Estimate (95% CI)	p-value
PS					
6 months	501	−0.39 (−1.78, 1.01)	0.584	−0.61 (−2.05, 0.83)	0.405
1 year	544	−0.66 (−1.92, 0.60)	0.307	−0.81 (−2.11, 0.48)	0.218
2 years	331	−0.95 (−2.27, 0.37)	0.158	−0.83 (−2.24, 0.59)	0.250
3 years	247	−0.82 (−2.78, 1.14)	0.408	−0.49 (−2.52, 1.54)	0.633
PHQ-9					
6 months	538	−0.94 (−2.19, 0.31)	0.140	−0.86 (−2.17, 0.45)	0.198
1 year	590	−0.50 (−1.70, 0.70)	0.413	−0.49 (−1.73, 0.75)	0.441
2 years	363	0.10 (−1.21, 1.41)	0.877	0.70 (−0.68, 2.07)	0.319
3 years	256	−2.20 (−3.70, −0.69)	0.004*	−1.95 (−3.50, −0.39)	0.014*
EQ-5D					
6 months	567	0.01 (−0.03, 0.06)	0.590	0.01 (−0.04, 0.06)	0.746
1 year	623	0.04 (0.00, 0.08)	0.078	0.04 (0.00, 0.08)	0.075
2 years	371	−0.01 (−0.05, 0.03)	0.649	−0.02 (−0.06, 0.03)	0.452
3 years	259	0.01 (−0.04, 0.07)	0.654	0.00 (−0.06, 0.06)	0.967
T25FW					
6 months	593	0.07 (−0.36, 0.49)	0.753	0.11 (−0.29, 0.51)	0.584
1 year	662	0.22 (−0.11, 0.54)	0.188	0.26 (−0.05, 0.58)	0.097
2 years	412	−0.08 (−0.41, 0.25)	0.645	−0.05 (−0.37, 0.28)	0.764
3 years	297	0.15 (−0.28, 0.57)	0.500	0.14 (−0.27, 0.54)	0.514

For outcomes at 6 months, 1 year, 2 years, 3 years, the beta estimates are for adherence at 6 months, 1 year, 2 years, and 3 years, respectively. PS: Performance Scales; PHQ-9: Patient Health Questionnaire 9; EQ5D: European Quality of Life 5 Dimensions; T25FW: Timed 25-foot walk; CI: confidence interval.

Table 4. Patient reported reasons for missed doses.

General Reason	Count	Percentage
Forgot	311	30.0%
Patient choice	139	12.6%
Medication access problem	101	9.8%
General health problems	71	6.9%
Medication side effects	45	4.4%
Unknown	290	28%

The adherence rate in our cohort was considerably higher than in the above studies. There are a number of factors that may have contributed to this discrepancy, including that definitions of adherence have varied across studies. We required that ≥80% of doses be taken for the patient to be considered adherent, which is a more liberal criterion than other investigators have used, but one that we felt would be more reflective of real world practices by patients. To broaden our study's applicability, we also conducted a sensitivity analysis with adherence defined as missing no doses over the last 3 months, and found that adherence ranged from 69.4% to 71.5%. A significant association between several outcomes and adherence was also noted, mostly at the 2-year point. However, the anticipated strong correlation was not appreciated.

Treatment with DMT is known to reduce MS relapses, reduce new lesion formation, and lessen disability progression.[13] Hence, it is surprising that in our study only minimal differences were seen between the adherent and non-adherent populations. Two potential explanations should be considered. First, it is possible that patients may be able to achieve disease control with less frequent dosing than is recommended from the clinical trials experience. This hypothesis is not supported by previous research that showed adherent patients have better quality of life, fewer neuropsychological issues, a lower risk of relapse and lower health care utilization.[2,12] A second possibility is that our data, which was based on direct report from the patient to their clinician was contaminated by inaccuracies from the patient, which may have compromised the expected associations between adherence and outcomes.

Table 5. Pairwise Spearman correlations between the outcomes at all time points.

	Baseline	6 months	1 year	2 years	3 years
PS					
T25FW	0.53	0.57	0.53	0.54	0.56
EQ5D	−0.77	−0.75	−0.77	−0.80	−0.76
PHQ-9	0.73	0.74	0.75	0.73	0.64
T25FW					
EQ5D	−0.51	−0.48	−0.49	−0.56	−0.52
PHQ-9	0.36	0.38	0.34	0.33	0.35
EQ5D					
PHQ-9	−0.69	−0.72	−0.71	−0.71	−0.63

PS: Performance scales; T25FW: Timed 25-foot walk; EQ5D: European Quality of Life 5 Dimensions; PHQ-9: Patient Health Questionnaire 9.

Patient report is important because it is the easiest and most commonly used metric to assess DMT adherence in the clinical setting. However, there are potential pitfalls to relying heavily on patient report. The most obvious is that patients may not remember the number of missed doses or that missed doses even occurred. MS can cause cognitive dysfunction, which may impact reporting and unfortunately we did not have the data to adjust for this. Encouraging patients to keep a log of their medication use may be helpful and there are several smart phone applications that can be used to track DMT adherence and remind patients to take medication. Autoinjectors that electronically track DMT adherence and provide patients with injection reminders, such as the BETACONNECT® for interferon β-1b,[14,15] may provide more accurate adherence information with respect to injectable therapies.

Another possibility might be purposeful patient underreporting, perhaps out of feelings of guilt or because the patient does not wish to disappoint their care team. This effect was elegantly demonstrated in a clinical trial of an inhaled bronchodilator for treatment of chronic obstructive pulmonary disease.[16] In the study, 241 patients were given a nebulizer with the capability to monitor date and time of each discharge, but 106 were informed only that it would measure total medication used. Of these 106 patients, 30% actuated their inhalers more than 100 times in a 3-hour interval immediately prior to clinic appointments, suggesting they were dumping medication to appear adherent. Only one patient aware of the device's monitoring capabilities dumped their medication. An emphasis on the importance of honesty with respect to DMT adherence and avoiding behaviors that might be interpreted as rebuking the non-adherent patient may help to allay this issue.

Nonetheless, natural human behavior may continue to prompt some patients to misrepresent their medication adherence.

Some shortcomings of our study should be noted. First, this was a single-center study and reflects the experience at a single tertiary care center. Geographic and cultural differences between patient populations at other centers may limit the generalizability of our findings. Second, the study relied on data provided by the patient at clinic visits, which may have been influenced by a number of factors. However, this was also an important feature of the study, because this same patient reported adherence is the measure most commonly used by clinicians to make treatment decisions. Finally, it would have been informative to assess the relationship between adherence and disease activity including relapses or new MRI lesions, but we did not have this data available. Thus, our conclusions are limited to the association of patient reported adherence with patient reported outcomes and with the T25FW.

Strategies for MS DMT management are increasingly focusing on no evidence of disease activity as a treatment target in the hopes of minimizing long-term disability.[17] This strategy emphasizes the importance of switching patients with breakthrough disease activity to more aggressive therapies, which generally also entails increased risk. However, in the presence of breakthrough disease, it is important to consider DMT adherence as a potential explanation for inadequate disease control. Our study raises concern that patient reported DMT adherence may not always be reliable and emphasizes the importance of adopting approaches to maximize the accuracy of adherence reports. Such approaches may include asking the patient to keep a log of DMT dosing,

and establishing a relationship with the patient that encourages openness about DMT adherence.

Supplementary material

Supplementary material is available for this article online.

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