The Impact of Adherence to Disease-Modifying Therapies on Functional Outcomes in Veterans with Multiple Sclerosis

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ABSTRACT

BACKGROUND: Patients who adhere to their DMTs have lower rate of MS-related relapses and disability.

OBJECTIVE: We sought to determine the adherence rate to disease-modifying therapies (DMTs) and its impact on functional outcome(s) in veterans with multiple sclerosis (MS).

METHOD: We reviewed the electronic records of 279 veterans with MS who were periodically followed in our MS clinic. We compared 3 groups of patients, defined according to their adherence to DMTs (non-adherent; poorly adherent; adherent) on their effect on disability progression and time to sustained EDSS score of 6.

RESULTS: There were 148 (53%) veterans with MS who were non-adherent to any DMT medication(s) while of the 131 (47%) veterans who were taking medications, 118 (42%) had a good- and 13 (5%) had poor-adherence. The mean age at MS onset was 36.6 (± 11.2) and mean duration of MS for the sample was 24 ± 13.5 years. The mean initial EDSS and TFIM scores were 4.09 ± 2.9 SD and 104 ± 25.7 for the study sample. The change in MMSE, TFIM scores, and time to sustained EDSS score of 6 significantly favored the good- compared to the non-adherence group ($P < .01$).

CONCLUSION: This study suggests that veterans with MS who adhered to their DMTs had less decline in their MS-related cognition, disease severity and disability compared to non- and poorly-adherent groups even after adjusting for age, gender, MS duration, and type. Time to EDSS score of 6 was significantly prolonged in the good-adherence group.

KEYWORDS: Multiple sclerosis, adherence, functional outcomes

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that follows a variable course. MS mainly affects young adults with highest incidence between the ages of 20 and 40. Its etiology is multifactorial, with both genetic susceptibility and environmental exposure contributing to its pathogenesis.[1] MS remains an incurable disease, hence treatments are designed to modify disease progression or alleviate symptoms, using disease-modifying therapies (DMTs).

Adherence describes the extent to which a patient act in accordance with the prescribed timing, dosing, and frequency of medication administration. This study uses the term "adherence" rather than "compliance" because adherence better reflects the action required of the patient and avoids judgmental connotations associated with the term "noncompliance."[2] Maintaining adherence to therapies long-term for chronic medical conditions to help derive the maximum possible clinical benefit is challenging both for the provider and the patient.[3] Depending on the study and definition of adherence published adherence rates in patients with relapsing-remitting MS have varied between 41% and 88%.[4-7] Adherence rates reported for different injectable DMTs vary from 79% to 85% for once weekly interferon beta-1a (IM IFNb-1a) 49% to 78% for other injectable DMTs.[4] Adherence to DMTs provide the greatest benefit by preventing relapses and delaying disease progression in most patients, it does not prevent MS-related symptoms such as fatigue, depression, cognitive impairment, or neuropathic pain.[8,9] Patients adherent to DMTs experience higher quality of life,[4,5] require less frequent hospitalization, less use of health-care resources and have a lower medical cost.[9,10] Likewise, poor adherence has been associated with worsening morbidity, increased health care cost, and increased morality.[11] The risk of discontinuation of DMTs is highest within the first 6 to 12 months of starting treatment.[12-14] Multiple factors influence adherence to therapy which involves the patient, clinician, therapy, and health-care system (Table 1). Thus, adherence is a challenging problem to address. Most of the studies in MS have assessed the impact of adherence for a 12 to 24-month time period, which is insufficient,[15] been retrospective,[16,17] and in the setting of clinical trials which is less applicable to real world clinical practice.

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Table 1. Factor influencing adherence to medication.

The *patient-specific* factors include lack of involvement in the treatment-decision making process, being forgetful from cognitive impairment, depression, unrealistic expectations, poor health literacy, or the patient's personal attitude towards the disease or the medication.
Therapy-specific factors such as adverse events (eg, flu-like symptoms, injection-site reactions), perceived lack of efficacy,[18] or needle-phobia can result in non-adherence.
Clinician-specific factors such as prescription of complex and multidrug regimen, inadequate communication between the patient, family (caregiver) and his primary care clinician as to the medication benefit.[19]
Healthcare-specific factors such as medication copay, relationship between patient and healthcare provider, and socio-economic factors also compromise adherence.[11,12,20,21]

The common methods of identifying patients at risk for non-adherence have been by patient self-report, electronic drug monitors (pill bottles), or pharmacy claims data to measure gaps in supply. Patient self-report is the most practical method of identifying non-adherent patients in the context of clinical care, but overestimates adherence compared with objective methods such as electronic drug monitors and pharmacy claims data.

This study was conducted in a clinical setting among military veterans who are periodically followed in the MS clinic. It compared functional outcome(s) between veterans with MS who were adherent to their prescribed DMTs to those who were non-adherent as, to the best of our knowledge this issue has not been previously studied due largely to the length and completeness of observation needed.[18]

This study can inform the provision of care of veterans, who constitute 7% (22 million) of the US population, and they receive medical care irrespective of their socioeconomic status. Information gathered will improve the provision of care by informing veterans with MS in our program the advantage of being adherent to DMTs and its increase in the likelihood of improved functional outcome(s).

Methods

Participants

This retrospective, observational study uses data longitudinally collected on 279 veterans diagnosed with MS (using the McDonald et al[19] criteria) and periodically followed every 4, 8, and 12-months (annual) in our MS program at the Oklahoma City VA Medical Center (OKC VAMC) since 1/1/2000 to 12/31/2019. The OKC VAMC is an MS Regional Program as part of the VA MS Center of Excellence and provides MS specialty care with a continuum of acute, chronic, and long-term care services consistent with Veterans Health Administration policies. The MS clinic has a structured approach where all MS patients on initial and yearly follow-up visit undergo detail clinical evaluation which includes the type of DMTs they are on, functional outcome measures and employment status, neuroimaging and blood tests: complete blood count for lymphocyte count, blood chemistry for renal and liver functions, vitamin D level [25-Hydroxy], and JVC ab titers.

In this single-center study design, the inclusion criteria were complete electronic records on veterans regularly followed in our MS program including functional outcome measures and employment status. The exclusion criteria were incomplete electronic records, especially lack of documentation of both initial and final functional outcome measures and employment status.

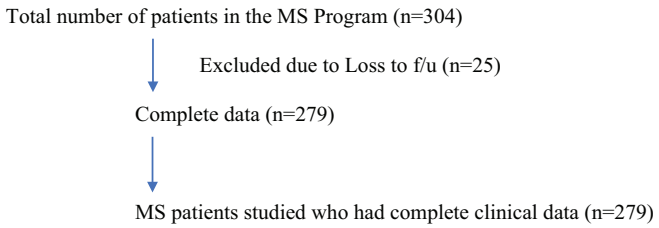

Figure 1. Total number of patients in the MS Program (n = 304).

(Flow chart (Figure 1)). Data collected included demographic and clinical measures (age, gender, race, height, weight), MS status (age at MS onset, clinical MS subtype (Relapsing-remitting (RR), Secondary-progressive (SP), and Primary-progressive (PP) MS),[20] duration of the disease), initial and annual documented cognition (Mini-Mental Status Examination (MMSE)), ambulatory distance achieved in 2-minutes (in feet, 2-MWT), presence of co-morbidities (hypertension, hyperlipidemia, diabetes mellitus, hypothyroidism, current smoking habit, alcohol use), and presence of MS related complications (fatigue, depression). Where the MS type changed from CIS/RIS to RRMS and RRMS to SPMS over the study period we kept those patients in their respective subtypes that is, RRMS and SPMS at the end of the study period. This study conforms to all STROBE guidelines and reports the required information accordingly (see Supplementary Checklist). This study was approved by the local Human Research Ethics Committee (IRB# 10366) and they determined that the study was exempt from patient consent due to retrospective review of the electronic medical records.

Intervention(s) or **treatment:** None

Investigators classified adherence to DMT use as (1) non-adherence; (2) good adherence; and (3) poor adherence. Investigators judged veterans to be non-adherent if they initially took but then stopped taking the prescribed DMTs or if they refused to take the prescribed DMTs to begin with due to adverse effects, because they perceived a lack of effect on their disease progress, or because they believed their disease was stable or progressive Investigators considered veterans to show

Good adherence if they took the prescribed DMT on regular basis as prescribed. Veterans were categorized as demonstrating poor adherence if they took prescribed DMT infrequently, missing 2 or more doses in a 4-week period on a regular basis. Investigators based this classification after inquiring verbally about everyone's DMT use during their face-to-face follow-up visits, subjectively checking at injection sites, where indicated and simultaneously verifying or cross-checked with their prescription refills data in the electronic medical records. Our facility pharmacy is the sole dispenser of DMT medications for our veterans with MS. Prescription refills in the VA system is by veteran generated request and veterans who are service connected have no copay for the medication refills compared to the general population. Switching between different DMTs (oral, injections, and infusions) was allowed when indicated after discussion between the provider and the patient. Where there were discrepancies between the veterans answer and prescription refill log further questions were asked during the evaluation about their DMTs use as to (i) how often they forget to take their medication, (ii) does the adverse effects impact the use of the medication, and (iii) what effect it has on their activities of daily living.

We used the 4 item self-report tool to predict pharmacy refill adherence as it is easy to administer in a clinical setting and has been validated with other self-report tools.[21] Prescription refills in the VA system is by veteran generated request and veterans who are service connected have no copay for the medication refills compared to the general population. Medication possession ratio (MPR) was calculated based on the pharmacy refill data. MPR was calculated as the sum of the days supply obtained between the first and the last pharmacy refill divided by the total number of days over 1-year. This clinical definition was supported by MPR cut score of < 0.8 equals non-adherence, 0.8 to 0.9 equals poor adherence, and 1.0 equals good adherence.[22]

Assessment study outcomes

Functional outcome measures were documented on initial and annual follow-up. Cognitive impairment was measured by Mini-Mental State Examination (MMSE);[23] MMSE is a widely used reliable and valid scale (score ranges from 0 to 30, higher the score lesser the cognitive impairment).[24] Level of disability was measured by annual Expanded Disability Status Scale (EDSS, (score ranges from 0 to 10, higher the score greater the MS-related physical disability),[25] total Functional Independence Measure (TFIM),[26] and 2-minute walk test (2-MWT) scores.[27] The TFIM is a reliable[28] and valid[29] functional assessment widely used in many rehabilitation settings to measure degree of disability (score ranges from 18 to 126, higher the score lesser the disability). A decline by 7-points on the TFIM score was considered an increase in disability.[30] The 2-MWT was adapted from the American Thoracic Society's 6-MWT protocol.[27] The 2-MWT is a valid, reliable, and sensitive measure of functional exercise capacity that is easy to administer,[31] time efficient and minimizes the effect of fatigue. The 2-MWT measures endurance by assessing walking distance over 2 minutes while moving at a comfortable speed using any ambulation aids (such as cane, walkers, and rollators) used in everyday life. Standing rest periods are allowed during the 2-minute walking evaluation. Conceptually, 2-MWT performance is associated with everyday tasks that require brief, but intense bouts of ambulation (eg, stair climbing or crossing the street). The 2-MWT has been shown to be a reliable and responsive measure of disability level and are strongly associated with community ambulation.[32] The distance covered (in feet) was measured using the Trumeter Mini-Measure Distance-Measuring Wheel, a device that accurately measures up to 10 000 feet. The EDSS, TFIM and 2-MWT scores were documented by a Board and TFIM certified clinician at the VA Medical Center.

Statistical analysis

1. Mean and standard deviation (SD) were summarized for continuous variables, while the count and percentage were reported for categorical variables. For non-normal distributed data, such as the count, median and inter quantile were summarized.
2. Continuous variables were compared between the groups (adherence vs non-adherence) using the analysis of variance (ANOVA) F-test or Kruskal-Wallis test depending on the data normality. Categorical variables were compared between the 2 groups using Chi-square test or Fisher exact test.
3. Time to EDSS 6 was examined using Cox proportional hazard (PH) regression. The follow up length between first available EDSS and first time EDSS $\geqslant 6$ of the 236 patients having EDSS follow up records was compared by the adherence groups. The hazard event for Cox PH was defined as the first observation of EDSS $\geqslant 6$. The hazard ratio with 95% confidence interval (CI) was reported for the 236 patients having EDSS follow up records by the adherence groups.
4. The linear mixed model (LMM) was employed to examine the association of MMSE, EDSS, FIM, and 2-min walk test score (as individual outcome) with patients' adherence group during the follow up respectively. For each of the association analyses, the effects of the age at entry, MS duration, MS type and severity (EDSS score) at admission were adjusted. Meanwhile, subjects with missing values of the adjusted variables were excluded.

Statistical significance was defined as a probability statistic $P < .05$ using a two-tailed analysis. Multiple testing problem was controlled by Bonferroni correction. Statistical analyses were performed using R 3.5 version (Vienna, Austria).

Results

Table 2 describes the study sample of 279 veterans with MS over a 19-year period. The mean age, duration of MS, and duration in the study for the sample was 51.8 ± 12.8 SD years (range 23-85 years), 24 ± 13.5 and 8.96 ± 3.88 years respectively. There were 224 (80%) men and 55 (20%) women. There were 115 (41%) in the RR and 120 (43%) in the Progressive MS patient. The initial EDSS and TFIM scores were 4.09 ± 2.9 SD and 104 ± 25.7. The 2-MWT for the whole study sample was 270 ± 160 ft.

Of the 279 patients with MS 148 patients (53%) were non-adherent to any DMTs, of the 131 (47%) patients with MS who took their DMTs, 118 (42%) had a good- and 13 (5%) had poor-adherence. When the MS patient with good-adherence was compared to the non-adherence group significant differences were seen at baseline in age of entry in years, duration of MS in years, gender, MS type, body mass index (BMI), and initial MMSE, EDSS and TFIM scores (< 0.001). Significant differences were also seen at baseline between the good- and the poor-adherence group for age of entry in years, duration of MS in years, and initial EDSS score (Table 2).

Table 3 presents the primary and secondary outcome measures between the groups. Change in MMSE, and TFIM scores significantly favored the good- compared to the non-adherence group ($P < .01$). Change in the MMSE, EDSS, and TFIM scores was non-significant between the good- and the poor-adherence group; however, the good-adherence group had less drop in the MMSE and TFIM scores and less increase in the EDSS score compared to the poor-adherence group. After adjusting for variables significant at baseline: age at entry, MS duration and type, and initial MS severity (based on EDSS score) MS patients in the good-adherence group had significantly less change in their EDSS score and TFIM scores ($P < .05$). Bonferroni correction for multiple testing found significant differences in the EDSS score favoring the good-adherence group. The Cox PH model identified significant difference of time to EDSS 6 in comparison of non- vs poor-adherence (*P*-value .002) and non- versus good-adherence (*P*-value $< .001$). The estimated hazard ratio was 0.5 (95% CI [0.357, 0.702]) comparing good- to non-adherence group, and 0.2 (95% CI [0.073, 0.551]) comparing poor- to non-adherence group. Thus, the risk of having an EDSS 6 score was 50% and 80% lower for the good and poor adherence groups respectively when compared to non-adherence group. No significant difference was seen between poor- and good-adherence groups (*P*-value 0.07).

Tables 4 and 5 presents functional outcomes for the 3-groups based on MS duration (⩽ and > 20 years). Significant differences in subjects with MS duration ⩽ 20 years favored the good- versus non-adherence group for the final EDSS (3.44 ± 2.59 vs 5.43 ± 3.07), and TFIM scores (115 ± 13.3 vs 95.3 ± 35.5) and 2-MWT in feet (371 ± 182 vs 256 ± 193) ($P < .001$). However, time to EDSS 6 score was not significant between the good- versus non-adherence group (2.08 ± 1.98 vs 2.88 ± 3.15) (*P* 0.43). Similarly, in subjects with MS duration of > 20 years there were significant differences which favored the good- versus non-adherence group for the final MMSE (28 ± 3.55 vs 25.3 ± 7.25), EDSS (5.59 ± 2.47 vs 7.35 ± 1.63), and TFIM scores (103 ± 21.3 vs 76.8 ± 33.9) and 2-MWT in feet (218 ± 187 vs 108 ± 144) ($P < 0.001$). Time to EDSS 6 score was significant between the good- versus non-adherence group (3.55 ± 4.05 vs 2 ± 2.79) (*P* 0.02).

Discussion

The main findings of our retrospective, observational study on the 19-year longitudinally collected data are: (i) 148 out of 279 (52%) of patients with MS stopped taking their DMTs (non-adherence) for several reasons which were: perceived lack of beneficial effect on the disease by the veteran over given time period, medication adverse effects specially injection site reactions and depression, and complain of having to take the DMT over a prolong time period. (ii) Of the veterans who took their DMTs as prescribed 10% (13/131) had poor-adherence due to be forgetful and/or being depressed. Similar rates of 30% to 50% of non-adherence was found among adults with chronic illness such as diabetes or hypertension.[33,34] Over the last 15 years, the rate of medication non-adherence has not appreciably changed.[33,34] (iii) Veterans with MS who had good-adherence when compared to veterans with non-adherence to their prescribed DMTs had better functional outcomes with a less drop in their MMSE cognitive score, MS-related disability TFIM score, and slower increase in MS-severity based EDSS score. Though no significant differences were noted in the functional outcome measures between good and poor-adherence groups which could reflect on the small sample size of the poor-adherence group, however; the change scores still favored the good-adherence group. When groups were compared controlling for MS duration (both ⩽ and > 20 years) good-adherence group had less MS-related cognitive and motor deficits, less MS-related severity and a prolong time to EDSS score 6.

When the groups were compared after controlling for significant baseline variables the positive effect of good-adherence group on functional outcome measures persisted. Based on the LMM, the poor-adherence group had an EDSS score 2.23 times less than the non-adherence group after adjusting other covariates. Meanwhile, the good-adherence group had an EDSS score 0.67 less than the non-adherence group. Less difference in the EDSS score times between the good- and the poor-adherence group compared to the non-adherence group may be explained by the small sample size of the poor-adherence group.

The present study has several limitations. First, this study primarily includes veterans who are men and non-Hispanic white (80%); thus, conclusions are less generalizable to the general population of MS patients. Second, the small sample size between the 3-adherence groups reduces

Table 2. Baseline demographics: Summary of data with test *P*-value for pairwise group comparison.

	OVERALL (N = 279)	NON-ADHERENT (N = 148, 53%)	GOOD-ADHERENCE (N = 118, 41%)	POOR-ADHERENCE (N = 13, 4.6%)	*P*-VALUE		
					NON VS POOR	NON VS GOOD	GOOD VS POOR
Age at MS onset (years)							
Mean (SD)	36.6 (±11.2)	37.3 (±11.9)	36.0 (±10.4)	34.3 (±10.5)	.386	.36	.58
Age @ entry (years)							
Mean (SD)	51.8 (±12.8)	54.9 (±13.1)	47.7 (±11.4)	54.6 (±12.1)	.944	<.001	.0415
Gender							
Women	55 (19.7%)	21 (14.2%)	30 (25.4%)	4 (30.8%)	.121	.0277	.741
Men	224 (80.3%)	127 (85.8%)	88 (74.6%)	9 (69.2%)			
Race							
American Indian or Alaskan native	6 (2.2%)	5 (3.4%)	1 (0.8%)	0 (0%)	.756	.0815	.831
Afro-American	44 (15.8%)	20 (13.5%)	21 (17.8%)	3 (23.1%)			
Hispanic	5 (1.8%)	1 (0.7%)	4 (3.4%)	0 (0%)			
Unknown	4 (1.4%)	4 (2.7%)	0 (0%)	0 (0%)			
White	220 (78.9%)	118 (79.7%)	92 (78.0%)	10 (76.9%)			
Duration of MS (years)							
Mean (SD)	24.0 (±13.5)	27.3 (±13.7)	19.4 (±11.6)	29.7 (±15.1)	0.556	<0.001	0.0039
Time in study (years)							
Mean (SD)	8.96 (±3.88)	9.95 (±3.65)	7.68 (±3.94)	9.38 (±2.29)	0.583	<0.001	0.128
MS type							
Relapsing remitting	115 (41.2%)	44 (29.7%)	61 (51.7%)	10 (76.9%)	.00745	.00725	.291
Progressive (primary and secondary)	120 (43.0%)	75 (50.7%)	43 (36.4%)	2 (15.4%)			
Other (CIS, RIS)	31 (11.1%)	19 (12.8%)	12 (10.2%)	0 (0%)			
Unclassified category	6 (2.2%)	4 (2.7%)	2 (1.7%)	0 (0%)			

(Continued)

Table 2. (Continued)

	OVERALL (N = 279)	NON-ADHERENT (N = 148, 53%)	GOOD-ADHERENCE (N = 118, 41%)	POOR-ADHERENCE (N = 13, 4.6%)	*P*-VALUE		
					NON VS POOR	NON VS GOOD	GOOD VS POOR
Number of chronical medical conditions*	2 [1, 3] Range [0, 8]	2 [1, 3] Range [0, 7]	2 [1, 3] Range [0, 8]	2 [1, 4] Range [1, 7]	.550	.769	.672
MMSE mean (SD)	27.1 (±4.58)	26.4 (±5.72)	27.8 (±2.76)	28.2 (±2.67)	.287	.0231	.626
EDSS mean (SD)	4.09 (±2.96)	4.94 (±2.96)	3.42 (±2.74)	1.73 (±2.01)	<.001	<.001	.0325
TFIM mean (SD)	104 (±25.7)	95.2 (±30.0)	112 (±17.3)	119 (±7.38)	.0109	<.001	.186
Hypertension (yes)	140 (50.2%)	79 (53.4%)	53 (44.9%)	8 (61.5%)	1	.127	.387
Diabetes mellitus (yes)	49 (17.6%)	27 (18.2%)	20 (16.9%)	2 (15.4%)	1	.746	1
Hyperlipidemia (yes)	146 (52.3%)	73 (49.3%)	64 (54.2%)	9 (69.2%)	.558	.794	.557
Body mass index mean (SD)	27.8 (±5.85)	27.1 (±6.12)	28.9 (±5.51)	26.3 (±4.72)	.643	.0192	.11
Current smoker (yes)	106 (38.0%)	63 (42.6%)	40 (33.9%)	3 (23.1%)	.146	.0935	.54
Alcohol overuse (yes)	11 (3.9%)	6 (4.1%)	4 (3.4%)	1 (7.7%)	.494	.747	.392
Depression (yes)	175 (62.7%)	92 (62.2%)	73 (61.9%)	10 (76.9%)	.545	.7	.372
Fatigue (yes)	177 (63.4%)	88 (59.5%)	80 (67.8%)	9 (69.2%)	.753	.784	1
DMT							
Infusion	18 (6.5%)	0 (0%)	18 (15.3%)	0 (0%)	<.001	<.001	.0362
Injectables	46 (16.5%)	2 (1.4%)	41 (34.7%)	3 (23.1%)			
Never/none/other	149 (53.4%)	145 (98.0%)	2 (1.7%)	2 (15.4%)			
Oral	66 (23.7%)	1 (0.7%)	57 (48.3%)	8 (61.5%)			

Abbreviations: DMT, disease modifying treatment; EDSS, expanded disability severity scale; MMSE, mini-mental state examination; TFIM, total functional independence measure.
*Median and inter quantile reported with KW test for group comparisons.

Table 3. Primary and Secondary Outcomes: Summary of data with test *P*-value for pairwise group comparison.

	OVERALL (N = 279)	NON-ADHERENT (N = 148)	GOOD-ADHERENCE (N = 118)	POOR-ADHERENCE (N = 13)	*P*-VALUE		
					NON VS POOR	NONE VS GOOD	GOOD VS POOR
MMSE							
Initial mean (SD)	27.1 (±4.58)	26.4 (±5.72)	27.8 (±2.76)	28.2 (±2.67)	.287	.0231	.626
Final mean (SD)	27.2 (±5.34)	25.6 (±7.20)	28.4 (±2.89)	29.0 (±1.22)	.095	<.001	.428
Change (F-I) mean (SD)	−0.124 (±3.60)	−0.805 (±4.30)	0.337 (±2.93)	0.846 (±2.27)	.18	.0329	.548
EDSS score							
Initial mean (SD)	4.09 (±2.96)	4.94 (±2.96)	3.42 (±2.74)	1.73 (±2.01)	<.001	<.001	.0325
Final mean (SD)	5.39 (±2.82)	6.89 (±2.20)	4.45 (±2.74)	3.23 (±2.45)	<.001	<.001	.128
Change (F-I) mean (SD)	1.10 (±1.77)	1.11 (±1.59)	1.04 (±1.88)	1.50 (±1.94)	.431	.798	.412
TFIM score							
Initial mean (SD)	104 (±25.7)	95.2 (±30.0)	112 (±17.3)	119 (±7.38)	.0109	<.001	.186
Final mean (SD)	96.9 (±30.3)	81.0 (±34.9)	109 (±18.6)	115 (±7.62)	.00119	<.001	.286
Change (F-I) mean (SD)	−5.89 (±17.5)	−9.92 (±21.6)	−2.61 (±12.8)	−3.50 (±10.9)	.359	.00544	.832
2-minute walk test							
Initial mean (SD)	270 (±160)	225 (±161)	304 (±156)	289 (±87.8)	.344	.00446	.814
Final mean (SD)	251 (±199)	155 (±174)	299 (±199)	347 (±98.4)	<.001	<.001	.432
Change (F-I) mean (SD)	11.0 (±118)	4.18 (±75.9)	12.2 (±138)	37.8 (±116)	.362	.753	.661
Time to EDSS 6 (years)	2.66 ± 3.30	2.01 ± 2.67	3.29 ± 3.71	5.5 ± 5.2	.002	<.001	.077

Abbreviations: DMT, disease modifying treatment; EDSS, expanded disability severity scale; MMSE, mini-mental state examination; TFIM, total functional independence measure.

Table 4. Primary and Secondary Outcomes: Summary of data with test *P*-value for pairwise group comparison in subjects with MS duration ⩽ 20 years.

	OVERALL (N = 120)	NON-ADHERENT (N = 48)	GOOD-ADHERENCE (N = 66)	POOR-ADHERENCE (N = 6)	*P*-VALUE		
					NON VS POOR	NONE VS GOOD	GOOD VS POOR
MMSE							
Initial mean (SD)	27.3 (±3.72)	26.7 (±5.17)	27.7 (±2.20)	27.5 (±3.56)	.723	.168	.831
Final mean (SD)	28.3 (±3.93)	26.8 (±7.07)	28.7 (±2.10)	29.2 (±0.983)	.437	.095	.565
Change (F-I) mean (SD)	0.679 (±2.44)	0.0526 (±2.53)	0.792 (±2.32)	1.67 (±3.14)	.210	.247	.401
EDSS score							
Initial mean (SD)	2.87 (±2.59)	3.37 (±2.76)	2.72 (±2.49)	0.833 (±0.753)	.031	.2	.071
Final mean (SD)	3.84 (±2.82)	5.43 (±3.07)	3.44 (±2.59)	2.25 (±2.23)	.028	.006	.284
Change (F-I) mean (SD)	0.870 (±1.77)	1.00 (±1.83)	0.768 (±1.72)	1.42 (±2.25)	.648	.618	.397

(Continued)

Table 4. (Continued)

	OVERALL (N = 120)	NON-ADHERENT (N = 48)	GOOD-ADHERENCE (N = 66)	POOR-ADHERENCE (N = 6)	*P*-VALUE		
					NON VS POOR	NONE VS GOOD	GOOD VS POOR
TFIM score							
Initial mean (SD)	113 (±19.8)	107 (±27.4)	115 (±13.2)	121 (±8.87)	.25	.049	.347
Final mean (SD)	110 (±22.9)	95.3 (±35.5)	115 (±13.3)	118 (±7.29)	.137	<.001	.588
Change (F-I) mean (SD)	−2.16 (±12.9)	−6.26 (±17.8)	−0.540 (±10.4)	−2.67 (±12.7)	.652	.102	.646
2-minute walk test							
Initial mean (SD)	327 (±143)	323 (±139)	333 (±148)	261 (±112)	.462	.756	.411
Final mean (SD)	342 (±186)	256 (±193)	371 (±182)	357 (±84.2)	.27	.023	.864
Change (F-I) mean (SD)	24.2 (±136)	10.8 (±80.6)	26.2 (±149)	54.3 (±163)	.493	.723	.755
Time to EDSS 6 (years)	2.81 (±3.03)	2.08 (±1.98)	2.88 (±3.15)	10.0 (±NA)	.003	.434	.037

Abbreviations: DMT, disease modifying treatment; EDSS, expanded disability severity scale; MMSE, mini-mental state examination; TFIM, total functional independence measure.

Table 5. Primary and Secondary Outcomes: Summary of data with test *P*-value for pairwise group comparison in subjects with MS duration > 20 years.

	OVERALL (N = 155)	NON-ADHERENT (N = 96)	GOOD-ADHERENCE (N = 52)	POOR-ADHERENCE (N = 7)	*P*-VALUE		
					NON VS POOR	NONE VS GOOD	GOOD VS POOR
MMSE							
Initial mean (SD)	26.9 (±5.16)	26.3 (±6.00)	27.8 (±3.37)	28.7 (±1.70)	.292	.096	.497
Final mean (SD)	26.6 (±5.99)	25.3 (±7.25)	28.0 (±3.55)	28.9 (±1.46)	.198	.016	.543
Change (F-I) mean (SD)	−0.634 (±4.10)	−1.04 (±4.67)	−0.167 (±3.44)	0.143 (±0.900)	.507	.271	.815
EDSS score							
Initial mean (SD)	5.06 (±2.85)	5.76 (±2.69)	4.31 (±2.80)	2.50 (±2.47)	.003	.003	.11
Final mean (SD)	6.44 (±2.29)	7.35 (±1.63)	5.59 (±2.47)	4.07 (±2.46)	<.001	<.001	.133
Change (F-I) mean (SD)	1.26 (±1.77)	1.15 (±1.52)	1.35 (±2.03)	1.57 (±1.81)	.496	.554	.786
TFIM score							
Initial mean (SD)	97.3 (±26.8)	90.1 (±28.7)	107 (±20.5)	116 (±5.03)	.045	<.001	.315
Final mean (SD)	88.7 (±31.6)	76.8 (±33.9)	103 (±21.3)	112 (±7.19)	.014	<.001	.314
Change (F-I) mean (SD)	−8.28 (±19.6)	−11.0 (±22.6)	−4.81 (±14.7)	−4.75 (±9.11)	.588	.105	.994
2-minute walk test							
Initial mean (SD)	182 (±145)	133 (±122)	232 (±156)	317 (±66.6)	.016	.013	.372
Final mean (SD)	177 (±178)	108 (±144)	218 (±187)	339 (±116)	<.001	.003	.128
Change (F-I) mean (SD)	−6.72 (±88.2)	0.0952 (±74.5)	−18.7 (±104)	21.3 (±81.1)	.651	.514	.536
Time to EDSS 6 (years)	2.60 (±3.40)	2.00 (±2.79)	3.55 (±4.05)	4.00 (±5.20)	.245	.022	.857

Abbreviations: DMT, disease modifying treatment; EDSS, expanded disability severity scale; MMSE, mini-mental state examination; TFIM, total functional independence measure.

the power to detect associations and may bias the result. Third, it is an observational study which reflects real world experience but the assigned groups were not by deliberate randomization. Fourth, cognition was only tested with MMSE, and none of the neuropsychological tests were used to assess other MS-related specific cognitive domains.[35] However, these neuropsychological tests despite high sensitivity are time consuming, expensive, and need a trained neuropsychologist to administer the test. Thus, a more cost-effective way to assess MS-related cognition in a clinical setting is needed.

Despite these limitations, the retrospective analysis of 19-years of longitudinally collected data, recruitment of all patients in the database with periodic follow-up at 4, 8, and 12-month time periods, with no loss and the completeness of the data captured by the standardized MS registry and the use of hospital pharmacy prescription dispensation administrative data to estimate adherence eliminated the potential for recall bias[36] provides a relevant rich and robust dataset to better understand how adherence to DMT affect level of cognition and disability in the veterans in the MS.

Though our MS-program has a multi-disciplinary team approach with emphasis on education, retraining, effective MS-symptom management, and aggressively addressing co-morbidities to improve functional outcomes including survival. Based on the study results we now hope to add a clinical pharmacist to our MS team to co-manage their medication adherence (including education, increase frequency of disease monitoring via telephone or in-person follow-up visits, and refill reminders). Effort is also made to simplify their medication regimen management (by reducing the frequency of their taking the injectables from a daily to weekly basis and where possible prescribe oral DMTs).

Conclusions

This study suggests the veterans who adhere to their DMTs are more likely to have a less decline in their level of cognition, MS-related severity and disability, compared to non- and poorly adherent groups even after adjusting for age, gender, MS duration, and type.

Authors Contributions

Dr. Meheroz H. Rabadi: Study concept and design. Data acquisition. Critical revision of the manuscript for important intellectual content. Study supervision. Ms. Kimberly Just: Data acquisition. Dr. Chao Xu: Analysis and interpretation. Critical revision of the manuscript for important intellectual content. Dr. Meheroz H. Rabadi report no disclosure. Ms. Kimberly Just report no disclosure. Dr. Chao Xu report no disclosure.

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Supplemental material

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