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Presence and Impact of Fatigue in Patients With Multiple Sclerosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Fatigue is common in multiple sclerosis (MS) and adversely affects function and quality of life. We examined clinical correlates of fatigue, its relationship with depression and sleepiness, and whether fatigue-related medications improve patient-reported outcomes.

Material/Methods: This single-center, longitudinal observational study retrospectively analyzed prospectively collected data from 203 veterans, categorized based on the presence or absence of fatigue. Primary outcomes were changes in the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), and Epworth Sleepiness Scale (ESS) from baseline to 12 months. Secondary outcomes included changes in the EuroQol 5-Dimension Questionnaire (EQ-5D), EQ visual analog scale (EQ-VAS), Total Functional Independence Measure (TFIM), Expanded Disability Status Scale (EDSS), 2-Minute Walk Test (2MWT), and Beck Depression Inventory (BDI). Medication exposure (amantadine, modafinil/armodafinil, methylphenidate/dextroamphetamine) was recorded.

Results: Fatigue was present in 134 of 203 (66%) and associated with higher body mass index (30.1 ± 5.5), hyperlipidemia (53.7%), diabetes (16.4%), higher BDI (4.58 ± 4.36) and ESS (10.7 ± 6.51), and worse EQ-5D VAS (all $P < 0.01$). Strong positive correlations were observed among fatigue (FSS/MFIS), depression (BDI), sleepiness (ESS), and disability (EDSS) scales ($P < 0.05$). Compared with no medication, fatigue-related medications did not improve FSS/MFIS or EQ-VAS scores; however, modest gains favored treated patients in TFIM change ($P = 0.04$) and 2MWT distance ($P = 0.02$). Post hoc comparisons across amantadine, modafinil/armodafinil, and amphetamine showed no between-drug differences in primary or secondary outcomes.

Conclusions: MS fatigue in veterans is highly prevalent and closely linked to metabolic comorbidities, depression, and sleep disturbance. Common fatigue medications provided no improvement in fatigue severity and quality of life.

Keywords: **Multiple Sclerosis • Veterans • Fatigue • Sleep • Depression • Quality Improvement**

Abbreviations: **BDI**, Beck Depression Inventory; **CBT**, cognitive behavior therapy; **ESS**, Epworth Sleepiness Scale; **EDSS**, Expanded Disability Status Scale; **EQ-5D**, European Quality of Life 5 Dimensions; **FSS**, Fatigue Severity Scale; **HRQoL**, health-related quality of life; **MFIS**, Modified Fatigue Impact Scale; **MS**, multiple sclerosis; **TFIM**, Total Functional Independence Measure; **VAS**, visual analog scale

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Introduction

Fatigue is one of the most prevalent and disabling symptoms in individuals with multiple sclerosis (MS). The Multiple Sclerosis Council defines fatigue as "a subjective lack of physical and mental energy interfering with usual activities as perceived by the individual or care provider." [1] Fatigue is reported in 75% to 85% of patients with MS, with approximately 25% describing it as a burdensome symptom that significantly affects daily functioning and quality of life [2-4].

Fatigue can be classified as central fatigue, due to reduced central drive to motor neurons [5], or peripheral fatigue, resulting from impaired muscle force generation [6]. The pathophysiology of MS-related fatigue remains poorly understood and is believed to be multifactorial. The primary mechanisms include central nervous system inflammation [7,8], demyelination, hypothalamic-pituitary-adrenal axis dysregulation, osmotic fluid shifts [9,10], and axonal loss [5]. The secondary mechanisms include pain, sleep, psychological conditions (eg, anxiety and depression), medication adverse effects, or physical inactivity [11,12]. Thus, fatigue is a multidimensional phenomenon encompassing physical, psychological, and emotional components [13] and is often unrelieved by rest.

Fatigue has been associated with increased cardiovascular risk, higher mortality, greater dependency on activities of daily living, and reduced quality of life [14,15]. Some patients even perceive fatigue management as critical to survival. Misconceptions about fatigue often lead patients to adopt prolonged bed rest, which leads to muscle atrophy and osteoporosis [10]. Conversely, physical activity has been shown to mitigate fatigue, enhance energy metabolism, and preserve muscle function [16]. Interventions such as Baduanjin, Pilates, yoga, aerobics, and resistance exercises have demonstrated efficacy in reducing fatigue symptoms, particularly among patients with chronic conditions, including those undergoing maintenance hemodialysis [17-21]. Cognitive behavioral therapy (CBT) has shown promise in promoting self-management of fatigue. Pharmacologic treatments, including amantadine, modafinil/armodafinil, methylphenidate, and amphetamine, are frequently prescribed off-label to help reduce the severity of fatigue in patients with MS. However, evidence supporting their efficacy is limited. For instance, a double-blind, placebo-controlled trial found modafinil was no more effective than a placebo in reducing fatigue severity [22,23].

Given the complexity and clinical significance of fatigue in MS, this study's primary aim was to identify the clinical correlates of fatigue in veterans with MS. The secondary aims were to evaluate the correlations between fatigue and depression, sleep disturbance, and disability measures, and explore the effectiveness of commonly prescribed fatigue-related medications on symptom relief, quality of life, disability, and mobility outcomes.

Material and Methods

Participants

This was a single-center, longitudinal, observational analysis conducted at the Oklahoma City Veterans Affairs Medical Center, a designated VA regional MS specialty program, using prospectively collected clinical data analyzed retrospectively. The study included veterans diagnosed with multiple sclerosis (MS) based on the McDonald criteria for MS [24] who had been followed in the MS clinic longitudinally (from 2010 onward). Through a multidisciplinary team approach, the clinic provides comprehensive MS care across all phases of the disease—acute, chronic, and long-term. Each patient encounter involves coordinated care from a team that includes a neurologist, physician assistant, dietician, psychologist, social worker, prosthetic department team member, clinic coordinator, and occupational, physical, and speech therapists. This team meets with each veteran in a single, integrated clinic visit, ensuring a holistic patient-centered approach to MS management.

Eligibility Criteria

The inclusion criteria required complete electronic medical records with data on fatigue and patient-reported quality-of-life assessments. The exclusion criteria included incomplete electronic medical records with missing data on fatigue and patient-reported quality-of-life assessments.

Patient Characteristics and Clinical Variables

The extracted demographic and clinical variables included age of symptom onset, age at initial evaluation, sex, race/ethnicity, MS subtype (relapsing-remitting, secondary progressive, primary progressive, clinically isolated syndrome, and radiologically isolated syndrome) [25], body mass index (BMI), initial Expanded Disability Scale Score (EDSS) [26], and Total Functional Independence Measure (TFIM) scores [27-31]. Fatigue was measured by the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) [32]. Data were collected on comorbidities known to influence disability in the general Oklahoma population, including hypertension, hyperlipidemia, diabetes mellitus, current smoking status, depression, and sleep disorders. Magnetic resonance imaging (MRI) of the brain and spinal cord documented the lesion locations. If no plaque lesions were seen on the MRI, it was documented as "normal". When only an outside MRI report indicated lesions consistent with MS and the original images were unavailable for review, MRI findings were classified as "missing".

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The use of medications for fatigue (amantadine, modafinil, amphetamine, and methylphenidate) was described as use or non-use. Medication exposure was based on the duration of the drug intake (12 months) before switching. In the VA system of care, the use of anti-fatigue medication escalates from amantadine to modafinil to dextroamphetamine after a 12-month use, while simultaneously addressing depression and sleep disorders if present. The medication component is an observational comparative analysis of treatment exposure rather than a test of efficacy.

This study was approved by the Oklahoma University Institutional Review Board (IRB# 18741). It was exempt from informed consent requirements, as it involved a retrospective analysis of prospectively collected standard care data. All data were de-identified and handled in accordance with institutional and federal guidelines to ensure patient confidentiality and data security.

Fatigue Status and Medication Exposure: Independent Variable

The study cohort consisted of 2 groups based on the presence or absence of fatigue, as determined by patient self-report or clinical inquiry documented in the medical record. The fatigue group was further stratified by whether they were on fatigue-related medications and, if so, by the type of medication prescribed, enabling a comparative analysis of treatment effects across different pharmacologic interventions.

Primary Outcome Variables

The primary outcomes were changes in the fatigue-related assessment scales—the FSS and the MFIS—recorded at baseline and at 12-month clinic follow-up, to evaluate the progression or improvement of fatigue symptoms over time, and the assessment of sleep disorders.

The Fatigue Severity Scale

The FSS consists of 9 items rated on a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree), evaluating the severity, frequency, and impact of fatigue on daily life. The final score is the average of all item responses [32]. The FSS emphasizes physical aspects of fatigue and has demonstrated good internal consistency, test-retest reliability, and discriminative validity in MS and other chronic conditions, including chronic fatigue immune dysfunction syndrome, systemic lupus erythematosus (SLE), chronic fatigue syndrome, and essential hypertension [32-34]. The FSS has good face validity and test-retest reliability. People with depression alone usually score about 4.5 points, while people with fatigue related to MS, SLE, or chronic fatigue immune dysfunction syndrome score an average of approximately 6.5 points. The FSS score has acceptable internal consistency, sensitivity to change [33], and discriminative ability [34] in patients with MS. A total score of 4 (36/9) or higher indicates fatigue.

The Modified Fatigue Impact Scale

The MFIS is a 21-item questionnaire assessing the impact of fatigue on physical (9 items), cognitive (10 items), and psychosocial (2 items) functioning. Each item is scored from 0 to 4, with a total score range of 0 to 84 [35]. A score of 39 of higher indicates fatigue [36]. If one scores high on the psychosocial subscale, then psychotherapy, such as CBT, may be recommended. If one scores high on the physical subscale range, then prescribing and adjusting the medication is recommended. The total MFIS score has a strong internal consistency (Cronbach's alpha of 0.81) [35] and test-retest reliability [36]. A change of 10 points is considered clinically meaningful [37]. The main shortcoming of both fatigue scales is their subjectivity. The scores are affected by mood, particularly depression, and therefore depression evaluation should be included when using fatigue scales.

Sleep Disorders

Sleep disorders, particularly obstructive sleep apnea, are known contributors to fatigue in patients with MS [11]. The Epworth Sleepiness Scale (ESS) is an 8-item questionnaire that measures daytime sleepiness. Each item is scored from 0 to 3, with a total score range of 0 to 24. A score of 10 or more suggests excessive sleepiness, and a score of 18 or more suggests severe sleepiness. For a score of 10 or more on ESS, a sleep study should be ordered, and the patient referred to a sleep specialist [38,39].

Secondary Outcome Variables

The secondary outcome measures assessed the impact of fatigue on quality of life, using the EuroQol 5-Dimension Questionnaire (EQ-5D) score and EQ visual analog scale (EQ-VAS); disability, using the TFIM and EDSS; and mobility, using the 2-Minute Walk Test (2MWT, measured in feet).

EQ-5D and EQ-VAS

The EQ-5D (version 2) evaluated the health state and health-related quality of life (HRQoL) of patients. This is a standardized, non–disease-specific questionnaire that assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with 3 response levels (no problem, some problems, and severe problems). The EQ-5D has established reliability and validity [40-43]. The EQ-VAS records the patient's self-rated health on a vertical scale from 0 ("worst

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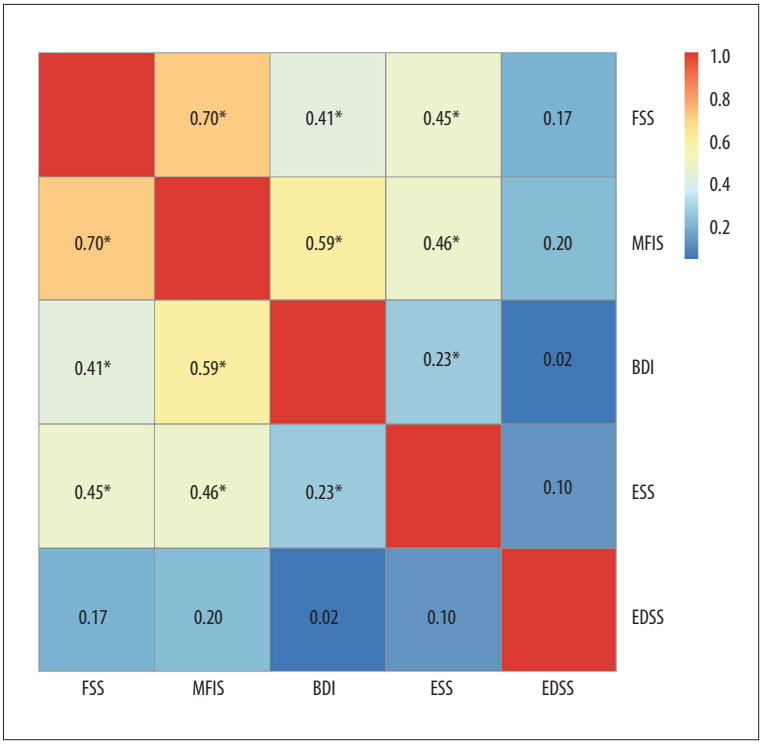

Figure 1. Correlation between Fatigue, Disability, Depression, and Sleep Scale scores. Values in each cell represent the Spearman correlation coefficient between the row and column variables. Asterisk indicates the significant correlation after Bonferroni correction at the level of 0.05. Abbreviations: FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; ESS, Epworth Sleepiness Scale; BDI, Beck Depression Inventory; EDSS Expanded Disability Status Scale.

imaginable health") to 100 ("best imaginable health") [44]. The patients completed the scale at their initial visit and at the 12-month in-clinic follow-up.

Total Functional Independence Measure

The TFIM measured the degree of disability [27]. It is a reliable [27] and valid [28] functional assessment measure widely used in rehabilitation settings [29]. The TFIM is an 18-item scale assessing functional independence across motor (13 items) and cognitive (5 items) domains. Each item is scored from 1 (total assistance needed) to 7 (complete independence, the patient performs 100% of the task), with a total score range of 18 to 126. A change in the TFIM score of 11 points or greater is considered clinically significant [30,31]. The patients completed the TFIM scale at their initial visit and at the 12-month in-clinic follow-up.

2-Minute Walk Test

The 2MWT was adapted from the American Thoracic Society 6-Minute Walk Test protocol [45]. The 2MWT measures the distance (in feet) a patient can walk in 2 minutes using their usual assistive devices. It is a valid, reliable, and time-efficient measure of functional exercise capacity and community ambulation [46,47]. Distance was measured using a Trumeter Mini-Measure Distance-Measuring Wheel. Standing rest periods are allowed as needed during the 2-minute walking evaluation.

Beck Depression Inventory

The BDI is a self-report inventory assessing the severity of depressive symptoms [48]. Depression is a known confounder of fatigue and was included to control for its influence on fatigue scores [49,50].

Correlation analysis included the relationships between fatigue and other clinical measures, specifically depression, sleep disturbances, and disability. These correlations were evaluated and presented in a matrix format to illustrate the associations among fatigue, depression, sleepiness, and disability scales (**Figure 1**).

Statistical Analysis

We report the mean ± standard deviation (SD) or median (25% percentile [Q1], 75% percentile [Q3]) for the continuous variables, depending on the normality check by the Shapiro test at a level of 0.05. Continuous variables were compared between the 2 groups using the *t* test or the Wilcoxon rank test, depending on the normality check.

Nominal variables between the 2 groups were compared using the chi-square test or Fisher exact test when cell counts were small (ie, more than 20% cells had expected counts < 5). Variables tested by the Fisher exact test were labeled in each table footnote. The Spearman correlation coefficient was used to evaluate pairwise associations between fatigue scores (FSS,

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Table 1. Variables between patient groups based on the absence or presence of fatigue (mean ± SD or median [Q1, Q3]).

Grouping variable	Total population (n = 203)	Nonfatigue (n = 69)	Fatigue (n = 134)	*P* value
Age in years	48.1 (± 11.4)	48.9 (± 12.2)	47.6 (± 11.0)	0.462
Age of onset in years	36.0 [28.0, 43.0]	36.0 [27.0, 42.0]	35.0 [28.0, 43.0]	0.637**
Duration of disease in years	8.00 [2.00, 16.0]	9.00 [2.00, 17.3]	8.00 [3.00, 16.0]	0.626**
Sex, men	146 (71.9%)	50 (72.5%)	96 (71.6%)	> 0.999
Sex, women	56 (27.6%)	19 (27.5%)	37 (27.6%)	
Race				
White	150 (73.9%)	49 (71.0%)	101 (75.4%)	0.836*
Black	42 (20.7%)	17 (24.6%)	25 (18.7%)	
Hispanic	7 (3.4%)	2 (2.9%)	5 (3.7%)	
Other	3 (1.5%)	1 (1.4%)	2 (1.5%)	
Missing	1 (0.5%)	0 (0%)	1 (0.7%)	
Multiple sclerosis type				
Clinically isolated syndrome	10 (4.9%)	5 (7.2%)	5 (3.7%)	0.756*
Primary progressive	40 (19.7%)	12 (17.4%)	28 (20.9%)	
Radiologically isolated syndrome	10 (4.9%)	2 (2.9%)	8 (6.0%)	
Relapsing progressive	9 (4.4%)	4 (5.8%)	5 (3.7%)	
Relapsing-remitting	112 (55.2%)	37 (53.6%)	75 (56.0%)	
Secondary progressive	16 (7.9%)	6 (8.7%)	10 (7.5%)	
Normal	2 (1.0%)	1 (1.4%)	1 (0.7%)	
Lesion location				
Brainstem	16 (7.9%)	10 (14.5%)	6 (4.5%)	0.096*
Cerebral hemisphere (CH)/cortical	95 (46.8%)	30 (43.5%)	65 (48.5%)	
Combined (CH and spinal cord)	33 (16.3%)	11 (15.9%)	22 (16.4%)	
Optic Nerve	1 (0.5%)	1 (1.4%)	0 (0%)	
Spinal cord (cervical, thoracic)	3 (1.5%)	1 (1.4%)	2 (1.5%)	
Normal	2 (1.0%)	0 (0%)	2 (1.5%)	
Missing	53 (26.1%)	16 (23.2%)	37 (27.6%)	
Hypertension	86 (42.4%)	25 (36.2%)	61 (45.5%)	0.164
Hyperlipidemia	97 (47.8%)	25 (36.2%)	72 (53.7%)	0.010
Diabetes mellitus	25 (12.3%)	3 (4.3%)	22 (16.4%)	0.012*
Body mass index	29.2 (±5.38)	27.5 (±4.66)	30.1 (±5.53)	< 0.001
Smoking	50 (24.6%)	14 (20.3%)	36 (26.9%)	0.327
Alcohol	9 (4.4%)	4 (5.8%)	5 (3.7%)	0.722*
Recreational drug use	621 (10.3%)	6 (8.7%)	15 (11.2%)	0.662

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Table 1. Variables between patient groups based on the absence or presence of fatigue (mean±SD or median [Q1, Q3]).

Grouping variable	Total population (n = 203)	Nonfatigue (n = 69)	Fatigue (n = 134)	*P* value
Mini-Mental State Examination	28.0 [27.0, 29.0]	28.0 [27.0, 29.0]	28.0 [27.0, 29.0]	0.426**
Motor upper extremity	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	0.599**
Motor lower extremity	5.00 [4.00, 5.00]	5.00 [4.00, 5.00]	5.00 [4.00, 5.00]	0.244**
Initial ambulation distance (feet/min)	390 [260, 390]	390 [260, 410]	390 [260, 390]	0.446**
Initial pain score (0-10 scale)	0 [0, 5.00]	0 [0, 4.00]	0 [0, 5.00]	0.279**
Initial spasticity score (MAS 0-5)	0 [0, 0]	0 [0, 1.00]	0 [0, 0]	0.319**
Depression	88 (43.3%)	38 (55.1%)	50 (37.3%)	0.026
Sleep disorder	91 (44.8%)	35 (50.7%)	56 (41.8%)	0.002
Initial Expanded Disability Scale Score (EDSS)	2.00 [1.00, 6.00]	2.00 [1.00, 6.00]	2.00 [1.00, 6.00]	0.530**
Initial Fatigue Severity Scale (FSS)	44.0 [30.5, 55.0]	33.5 [14.0, 44.3]	46.0 [35.5, 56.5]	<0.001**
Initial Modified Fatigue Impact Scale (MFIS)	42.9 (± 18.3)	30.9 (± 16.5)	47.4 (± 16.9)	<0.001
Cognitive subscore	18.0 [10.0, 25.0]	12.0 [3.00, 19.0]	21.0 [13.0, 27.0]	<0.001**
Physical subscore	21.0 [14.0, 27.0]	16.0 [10.0, 22.0]	23.5 [16.0, 29.0]	<0.001**
Psychosocial subscore	4.00 [3.00, 6.00]	3.00 [1.00, 4.00]	4.00 [3.00, 6.00]	0.001**
Initial Epworth Sleep Scale (ESS)	9.00 [5.00, 15.0]	6.00 [3.50, 9.50]	10.0 [5.00, 16.0]	0.002**
Initial Beck Depression Inventory	3.00 [0, 6.00]	1.00 [0, 3.00]	4.00 [1.00, 7.00]	<0.001**
Initial EuroQol 5 Domain (EQ-5D)	9.00 [7.00, 10.0]	7.00 [6.00, 9.00]	9.00 [8.00, 10.0]	<0.001**
Initial EuroQol visual analog scale (EQ-VAS)	72.0 [60.0, 85.0]	81.5 [65.0, 90.0]	70.0 [55.0, 84.0]	0.002**
Initial Total Functional Independence Measure score	120 [113, 124]	120 [112, 124]	120 [113, 124]	0.766**

* Fisher exact test due to small cell counts. ** Wilcoxon rank test due to non-normally distributed data, according to the Shapiro normality test.

MFIS), depression (BDI), sleepiness (ESS), and quality-of-life measures (EQ-5D, EQ-VAS).

A significance level of 0.05 after Bonferroni correction was used to adjust for multiple comparisons in the pairwise correlation tests presented in **Figure 1**. Correlation strength was interpreted using standard thresholds (eg, 0.1-0.3 = weak, 0.4-0.5 = moderate, ≥ 0.6 = strong).

Repeated measurements using change scores from baseline to follow-up were analyzed. For fatigue and functional outcomes measured at baseline and follow-up, individual change scores were calculated for each patient as the difference between follow-up and baseline values. These change scores were then used as the primary outcome for between-group comparisons and were analyzed using the same statistical methods described for continuous variables.

A complete case analysis was conducted for the analysis. All statistical analyses were performed using R software (v4.0.3, Vienna, Austria).

This study conforms to all STROBE guidelines and reports the required information accordingly.

Results

Table 1 presents the baseline demographics of the study sample (n = 203). The cohort was 72% male, with a mean age at disease onset of 37.1 ± 11.2 years (range, 18-70) and a mean disease duration of 10.9 ± 10.4 years (range, 0-49). The mean baseline EDSS score was 3.0 ± 2.64. MS-related fatigue was reported in 134 patients (66%).

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Table 2. Primary outcomes in multiple sclerosis patients with fatigue by medication status (mean ± SD or median [Q1, Q3]).

	Total (n = 134)	No (n = 77)	Yes (n = 57)	*P* value
Initial FSS	46.0 [35.5, 56.5]	46.5 [38.5, 58.0]	46.0 [34.5, 56.0]	0.377**
12-month FSS	45.0 [32.0, 52.0]	45.0 [33.0, 51.0]	45.5 [31.5, 52.5]	0.741**
Change FSS	-1.65 (±15.8)	-2.38 (± 13.2)	-1.00 (± 17.9)	0.729
Initial MFIS	47.4 (±16.9)	46.5 (± 16.9)	48.6 (± 17.0)	0.494
Initial MFIS, cognitive	20.0 (±8.93)	18.8 (± 9.02)	21.5 (± 8.68)	0.142
Initial MFIS, physical	23.5 [16.0, 29.0]	22.5 [15.0, 29.0]	24.5 [16.8, 29.0]	0.666**
Initial MFIS, psychosocial	4.00 [3.00, 6.00]	4.00 [3.00, 6.00]	5.00 [3.00, 6.00]	0.877**
12-month MFIS	48.6 (± 17.1)	46.3 (± 16.5)	50.6 (± 17.7)	0.284
12-month MFIS, cognitive	20.8 (± 9.36)	18.5 (± 8.71)	22.7 (± 9.59)	0.074
12-month MFIS, physical	22.8 (± 8.05)	22.6 (± 8.46)	23.0 (± 7.81)	0.844
12-month MFIS, psychosocial	5.00 [2.00, 6.00]	4.00 [2.00, 6.00]	5.00 [3.00, 6.75]	0.324**
Change MFIS	0 [-7.00, 9.00]	1.00 [-11.0, 10.0]	-2.00 [-6.50, 7.50]	> 0.999**
Change the MFIS, cognitive	-0.519 (± 7.62)	-0.423 (± 8.10)	-0.615 (± 7.28)	0.929
Change MFIS, physical	-0.811 (± 8.46)	-1.46 (± 9.16)	-0.185 (± 7.84)	0.589
Change MFIS, psychosocial	0 [-2.00, 1.00]	-1.00 [-2.00, 0]	0 [-1.00, 1.00]	0.390**
Initial ESS	10.0 [5.00, 16.0]	10.0 [5.00, 16.0]	9.50 [5.00, 17.0]	0.746**
12-month ESS	9.99 (± 5.99)	9.65 (± 5.17)	10.3 (± 6.68)	0.649
Change ESS	0.0694 (± 5.96)	0.206 (± 6.09)	-0.0526 (± 5.92)	0.856

* Fisher's Exact test due to small cell counts. ** Wilcoxon rank test due to non-normally distributed data, according to the Shapiro normality test. Abbreviations: ESS, Epworth Sleep Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale.

Normality testing using the Shapiro-Wilk test was performed for all continuous variables. Due to the large number of variables, detailed results are provided in the table footnotes. Overall, several variables deviated from normality, supporting the use of nonparametric analyses.

Compared with patients without fatigue, patients with fatigue showed higher BMI (30.1 ± 5.53 vs 27.5 ± 4.66) and a higher rate of hyperlipidemia (53.7% vs 36.2%) and diabetes mellitus (16.4% vs 4.3%). They had higher baseline scores on the BDI (4.58 ± 4.36 vs 2.12 ± 2.72; $P < 0.001$) and ESS scores (10.7 ± 6.51 vs 7.11 ± 4.74; $P < 0.002$), and worse FSS/MFIS scores ($P < 0.0001$), with lower quality of life measure scores on the EQ-5D (9.01 ± 2.23 vs 7.43 ± 1.89) and EQ-VAS 67.8 ± 19.5 vs 78.7± 15.9 ($P < 0.001$).

Given the observational design and baseline differences, there was an absence of observed improvement in primary outcome measures (change in FSS, MFIS total and subscale scores, and ESS) between the treated and untreated groups ($P > 0.05$; **Table 2**).

An absence of observed improvement was seen in the secondary outcome measures (change in the EQ-5D, EQ-VAS, TFIM total and subscales, ambulation distance [2MWT], and EDSS), which were largely similar between the treated and untreated groups ($P > 0.05$). However, treated patients had better TFIM change scores (-2.53 ± 15.9 vs -7.15 ± 14.9; $P = 0.044$) and improved 2MWT ambulation distance (35.1 ± 105 vs -22.3 ± 120; $P = 0.020$; **Table 3**).

Post hoc comparison among amantadine, modafinil/armodafinil, and amphetamine showed no between-drug differences across the primary and secondary outcome measures ($P > 0.05$; **Tables 4, 5**).

Spearman coefficients indicated moderate-to-strong positive associations among fatigue (FSS/MFIS), depression (BDI),

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Table 3. Secondary outcomes in multiple sclerosis patients with fatigue by medication status (mean ± SD or median [Q1, Q3]).

	Total (n = 1 34)	No (n = 77)	Yes (n = 57)	*P* value
Initial EQ-5D	9.00 [8.00, 10.0]	9.00 [7.75, 11.0]	9.00 [8.00, 10.0]	0.591**
12-month EQ-5D	9.00 [7.50, 10.0]	9.00 [8.00, 10.0]	8.50 [6.25, 10.0]	0.343**
Change EQ-5D	0 [-1.00, 1.00]	0 [-1.00, 1.00]	0 [-1.00, 1.00]	0.818**
Initial EQ-VAS	70.0 [55.0, 84.0]	60.0 [50.0, 80.0]	75.0 [65.0, 86.0]	0.018**
12-month EQ-VAS	67.8 (± 16.2)	67.4 (± 13.1)	68.0 (± 18.7)	0.886
Change EQ-VAS	-1.08 (± 20.0)	3.76 (± 21.3)	-5.77 (± 17.8)	0.068
Initial TFIM	120 [113, 124]	120 [113, 124]	121 [114, 125]	0.404**
12-month TFIM	119 [106, 123]	116 [106, 123]	120 [109, 123]	0.427**
Change TFIM	-2.00 [-5.50, 1.00]	-3.00 [-9.00, 0]	-1.00 [-4.00, 3.00]	0.044**
Initial EDSS	2.00 [1.00, 6.00]	1.50 [1.00, 6.00]	2.00 [1.00, 6.00]	0.484**
12-month EDSS	6.00 [2.00, 6.50]	6.00 [2.00, 6.50]	6.00 [2.00, 6.00]	0.447**
Change EDSS	1.00 [0, 2.50]	1.00 [0, 4.00]	1.00 [0, 2.00]	0.810**
Initial ambulation 2MWT in feet	390 [260, 390]	346 [260, 390]	390 [260, 390]	0.997**
12-month ambulation 2MWT in feet	363 [180, 461]	330 [133, 438]	410 [260, 470]	0.095**
Change ambulation 2MWT in feet	0 [-50.0, 60.0]	-15.5 [-60.0, 25.0]	40.0 [-22.5, 113]	0.020**

* Fisher exact test due to small cell counts. ** Wilcoxon rank test due to non-normally distributed data, according to the Shapiro normality test. Abbreviations: EQ-5D, EuroQol 5 Domain; VAS, visual analog scale; EDSS, Expanded Disability Scale Score; TFIM, Total Functional Independence Measure; 2MWT, 2-Meter Walk Test.

sleepiness (ESS), and disability (EDSS) scales ($r \approx 0.23$-0.70; $P < 0.05$ after Bonferroni). All exact correlation coefficients are presented in a matrix format in **Figure 1**.

Discussion

This prospectively collected, retrospectively analyzed longitudinal study in a predominantly male VA cohort demonstrated the following. (1) A high prevalence of fatigue was reported in 66% of patients, highlighting its role as one of the most common and burdensome symptoms in MS. (2) Patients experiencing fatigue had significantly higher rates of comorbidities (hyperlipidemia, diabetes mellitus, and higher BMI) suggesting a potential link between metabolic health and fatigue severity in MS. (3) No clinical improvement was seen between the treated and untreated fatigue-related medication group for primary and secondary outcome measures, except for disability measures (TFIM and distance ambulated), which favored the treated group. This observational comparative analysis of exposure to commonly prescribed fatigue medications (amantadine, modafinil/armodafinil, amphetamine) found no meaningful improvement in fatigue severity or HRQoL compared with no pharmacotherapy, although small advantages were observed in functional measures (TFIM and ambulation). (5) A moderate-to-strong correlation was found between fatigue, depression, sleep disturbance, and MS-related disability scores, highlighting the multifactorial and interconnected nature of fatigue, affect, and sleep disturbance in MS.

Fatigue is among the most disabling and prevalent symptoms in patients with MS, with a prevalence of 53% to 92%, depending on the definition and assessment tools used [51]. In this study, 66% of patients with MS reported fatigue, aligning with prior prevalence estimates. No specific anatomical MS lesion locations on neuroimaging are significantly associated with fatigue [52]. However, in a prior study, DeLuca et al examined 15 patients with MS and 15 healthy controls using functional MRI after 4 trials of a behavioral task assessing processing speed (modified Symbol Digit Modalities Test) and found that patients with MS exhibited increased activation in the basal ganglia, frontal lobe regions (superior, medial, middle, and inferior), parietal regions (precuneus and cuneus), thalamus, and occipital lobes compared with healthy controls [53]. Likewise, in their study of 41 patients with relapsing-remitting MS with mild disability and 20 healthy controls, using proton magnetic resonance spectroscopy, Tellez et al found that the basal ganglia involvement contributed to the development of MS-related fatigue [54].

The strong correlation between the 2 validated fatigue scales in this study underscores the reliability of fatigue measures

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Table 4. Primary outcomes in multiple sclerosis patients with fatigue by type of medication prescribed (mean, SD).

	Total (n = 59)	Amantadine (n = 10)	Modafinil (n = 43)	Amphetamine (n = 6)	*P* value
Initial FSS	50.0 [36.0, 56.3]	53.0 [44.3, 58.3]	49.5 [36.0, 56.3]	52.0 [43.8, 55.8]	0.892**
12-month FSS	48.0 [42.0, 50.0]	33.0 [25.3, 45.0]	49.0 [44.0, 50.0]	44.0 [38.8, 49.5]	0.359**
Change FSS	-2.64 (± 15.1)	-9.75 (± 15.1)	-0.150 (± 14.3)	-8.00 (± 20.0)	0.397
Initial MFIS	48.6 (± 17.3)	43.3 (± 19.8)	49.9 (± 16.8)	49.7 (± 17.4)	0.569
Initial MFIS, cognitive	21.0 (± 9.04)	16.0 (± 11.2)	21.7 (± 8.57)	24.0 (± 8.52)	0.304
Initial MFIS, physical	23.5 (± 8.26)	21.3 (± 10.7)	23.8 (± 8.10)	24.3 (± 7.14)	0.795
Initial MFIS, psychosocial	4.00 [3.00, 6.00]	3.50 [2.25, 4.75]	4.00 [3.00, 6.00]	5.50 [5.00, 6.25]	0.253**
12-month MFIS	48.7 (± 17.3)	40.8 (± 19.6)	50.8 (± 18.4)	46.3 (± 10.8)	0.539
12-month MFIS, cognitive	22.0 (± 9.42)	16.0 (± 4.97)	23.4 (± 9.90)	20.8 (± 9.25)	0.355
12-month MFIS, physical	23.8 (± 7.44)	21.3 (± 12.5)	24.3 (± 6.55)	23.5 (± 7.90)	0.760
12-month MFIS, psychosocial	4.62 (± 2.21)	3.50 (± 3.42)	4.71 (± 2.15)	5.25 (± 0.957)	0.516
Change MFIS	0.0313 (± 16.0)	-0.500 (± 36.5)	1.05 (± 12.7)	-3.33 (± 9.37)	0.844
Change MFIS, cognitive	-1.81 (± 7.83)	-4.33 (± 13.3)	-1.27 (± 7.70)	-2.00 (± 3.00)	0.839
Change MFIS, physical	-2.05 (± 7.22)	-8.00 (± 14.1)	-1.00 (± 6.11)	-1.67 (± 2.52)	0.318
Change MFIS, psychosocial	-0.500 [-1.00, 0]	0 [-2.50, 0]	-0.500 [-1.25, 1.00]	-1.00 [-1.00, -0.50]	0.887**
Initial ESS	-	9.00 [4.00, 12.5]	11.0 [6.00, 17.3]	14.5 [5.25, 20.0]	0.441**
12-month ESS	8.50 [4.00, 16.0]	3.50 [2.75, 7.75]	8.50 [4.50, 15.8]	13.0 [6.75, 16.3]	0.434**
Change ESS	-1.53 (± 5.83)	-2.50 (± 5.45)	-1.64 (± 6.31)	-0.500 (± 4.85)	0.866

** Kruskal-Wallis test due to non-normally distributed data, according to the Shapiro normality test. Abbreviations: ESS, Epworth Sleep Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale.

and the multidimensional nature of fatigue in MS. The presence of depression and sleep disturbances with fatigue suggests either a common underlying mechanism or a bidirectional relationship among these symptoms, as supported by prior literature [32].

Despite the high prevalence and impact MS-related fatigue, effective treatment options remain limited. In this study, commonly prescribed fatigue medications (amantadine, modafinil/armodafinil, amphetamine) did not meaningfully improve fatigue severity or HRQoL compared with no pharmacotherapy, although small advantages were observed in the functional measures TFIM and ambulation. While amantadine showed the greatest numerical improvement and modafinil the least, these findings may be confounded by the small sample sizes in the amantadine and amphetamine groups (≤ 10 patients), compared with modafinil (n = 43). In the COMBO-MS randomized trial, which included 336 participants with MS-related fatigue, when randomly assigned to modafinil (n = 107), CBT (n = 103), and combination (n = 108), similar reductions in fatigue scores (measured by MFIS) were observed at 3 months across all treatment arms [23]. Furthermore, in their study of 56 patients with MS-related fatigue, Smedal et al reported that fatigue was associated with HRQoL at baseline in patients undergoing inpatient physiotherapy. However, the improvement in fatigue was not associated with an improvement in HRQoL, highlighting the complex interplay between symptom relief and perceived well-being [55]. These findings align with prior mixed evidence and suggest that medication alone is insufficient; optimizing metabolic health, sleep disorders (eg, obstructive sleep apnea), and depressive symptoms may be equally or more impactful [1,10]. Similarly, non-pharmacologic interventions such as CBT have shown limited efficacy [23].

This study had certain limitations. First, a modest sample size may bias the results, as it reduces the statistical power to detect significant associations and limits the generalizability of the results. Subgroup analyses comparing medication types included

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Table 5. Secondary outcomes in multiple sclerosis patients with fatigue by the type of medication prescribed (mean±SD or median [Q1, Q3]).

	Total (n = 59)	Amantadine (n = 10)	Modafinil (n = 43)	Amphetamine (n = 6)	*P* value
Initial EQ-5D	8.90 (± 2.24)	8.00 (± 2.71)	9.11 (± 2.14)	8.67 (± 2.42)	0.479
12-month EQ-5D	8.76 (± 2.10)	9.75 (± 2.06)	8.95 (± 2.09)	6.75 (± 0.957)	0.090
Change EQ-5D	0 [-1.00, 1.00]	1.00 [-0.250, 2.00]	0 [0, 0.250]	-2.00 [-3.75, -0.500]	0.181**
Initial EQ-VAS	70.0 [60.0, 90.0]	78.0 [65.0, 90.0]	70.0 [55.0, 85.0]	80.0 [75.0, 90.0]	0.283**
12-month EQ-VAS	70.0 (± 18.1)	74.3 (± 19.2)	68.4 (± 19.3)	73.8 (± 12.5)	0.773
Change EQ-VAS	0.407 (± 19.9)	9.75 (± 32.8)	-1.15 (± 18.3)	-1.67 (± 12.6)	0.614
Initial TFIM	121 [111, 125]	121 [110, 125]	121 [112, 125]	112 [108, 124]	0.678**
12-month TFIM	115 [103, 121]	119 [104, 120]	113 [103, 121]	117 [104, 122]	0.806**
Change TFIM	-3.00 [-12.0, 0]	-5.00 [-13.0, -1.00]	-4.00 [-12.0, -0.500]	3.00 [2.00, 5.00]	0.078**
Initial EDSS	2.50 [1.00, 6.00]	3.50 [1.63, 6.38]	3.00 [1.00, 6.00]	1.50 [1.00, 5.00]	0.706**
12-month EDSS	6.00 [3.00, 6.50]	6.50 [3.00, 6.50]	6.00 [3.00, 6.50]	4.50 [1.50, 6.38]	0.688**
Change EDSS	1.00 [0, 3.00]	1.00 [0.500, 1.00]	1.50 [0, 3.00]	0.750 [0, 1.88]	0.651**
Initial ambulation 2MWT in feet	260 [162, 390]	260 [163, 303]	260 [150, 390]	390 [260, 520]	0.161**
12-month ambulation 2MWT in feet	328 [148, 450]	321 [240, 420]	320 [140, 450]	440 [430, 480]	0.356**
Change ambulation 2MWT in feet	21.8 (± 125)	-9.67 (± 123)	19.3 (± 131)	70.0 (± 104)	0.581

**Kruskal-Wallis test due to non-normally distributed data, according to the Shapiro normality test. Abbreviations: EQ-5D, EuroQol 5 Domain; VAS, visual analog scale; EDSS, Expanded Disability Scale Score; TFIM, Total Functional Independence Measure

small sample sizes for certain groups (eg, amphetamines), which limits statistical power and increases the risk of type I and type II errors. Although nonparametric methods were used to account for small group sizes and potential violations of distributional assumptions, these approaches do not fully mitigate the limitations associated with sparse data. As a result, these subgroup comparisons should be considered exploratory, and the findings interpreted with caution. Larger studies are needed to validate the presented results. Second, the study lacked the quantification of brain lesion burden, as higher lesion burden across the brain can affect depression-related networks in MS, which may influence fatigue [56]. Third, although this study represents real-world data, the patients included were mainly non-Hispanic White men (96%) receiving high-quality, subsidized medical care through the Veteran Health System. These demographic and healthcare access factors limit the applicability of findings to the broader MS population, particularly in more diverse or underserved communities. The significance of this study's findings is directly applicable to veterans in a structured specialty MS care program and may not apply to broader community, female predominant, or diverse MS cohorts. Finally, fatigue was assessed using self-reported measures, which may introduce response bias and limit objectivity.

Despite these limitations, the study has several notable strengths. First, longitudinal (at least 12 months) follow-up allowed for the assessment of symptom persistence and temporal associations. Second, there was no loss to follow-up, ensuring a comprehensive dataset and reducing the risk of attrition bias.

Future research should incorporate functional MRI to explore network-level disruptions associated with fatigue in MS. Identifying specific neural circuits involved may help clarify the pathophysiology of fatigue and guide targeted interventions. Future studies should also test integrated interventions combining sleep optimization, mood treatment, exercise, and energy conservation strategies alongside disease-modifying therapy.

Conclusions

This study suggests that fatigue in veterans with MS is highly prevalent. The findings support cautious interpretation and reinforce the relevance of multimodal assessment of mood, sleep, and metabolic comorbidity. Finally, fatigue medication exposure was not associated with improvement in fatigue severity

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or quality-of-life measures over 12 months, while small differences were observed in selected functional outcomes.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data Access Statement

The data supporting the findings of this study are available from the corresponding author, Dr. Meheroz H. Rabadi [MHR], upon request. However, the data are not publicly available due to the restrictions imposed by the Veterans Health Authority, as they contain patient-sensitive information that could compromise participant's privacy. Any data sharing request will require prior approval from the Veterans Affairs Research & Development Committee and the University of Oklahoma Institutional Review Board (IRB).

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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