Patient Preference and Adherence

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ORIGINAL RESEARCH

Clinical Practice Evidence of Treatment Satisfaction with Moderate and High-Efficacy Drugs in Multiple Sclerosis

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Introduction: Generally, the choice of disease-modifying treatment (DMT) for people with multiple sclerosis (PwMS) is based on aspects of efficacy and safety. However, due to the diversity of drugs and the different routes of administration, it is essential to know the experience and satisfaction of PwMS. Patient- reported outcomes (PROs) help us to optimize and improve adherence.

Methods: Our objective with this cross-sectional, non-interventional study is to analyze satisfaction outcomes using the treatment satisfaction questionnaire for medication (TSQM) according to moderate or high efficacy of DMTs and the relationship with demographic, clinical and quality of life (QoL) aspects.

Results: PwMS receiving high-efficacy DMTs show greater overall satisfaction, but not in the other TSQM subscales. The route of administration did not show differences in treatment satisfaction. The best QoL scores were observed in patients treated with oral DMTs compared to injectables or infusions.

Discussion: The efficacy of DMT is a significant predictor of overall satisfaction. Quality of life has a minimal impact on overall satisfaction. EDSS, treatment duration and fatigue (MFIS) were not significant predictors of satisfaction outcomes. The knowledge provided by the PROs allows healthcare professionals to better understand the preferences and needs of PwMS, adjusting therapeutic strategies, improving patient experience and treatment effectiveness.

Keywords: quality of life, relapsing remitting multiple sclerosis, fatigue, patient- reported outcomes, treatment satisfaction, disease-modifying treatment

Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease that affects the central nervous system (CNS), causing demyelination and neuronal injury. MS is the most common cause of non-traumatic disability among individual aged 18 to 40. The progression of the disease, along with the accumulation of physical and cognitive disability, leads to a decline in the quality of life of people with multiple sclerosis (PwMS).[1]

Disease-modifying treatments (DMTs) are currently available. They are classified according to the efficacy demonstrated in clinical trials into: moderate-efficacy DMT (ME-DMT) and high-efficacy DMT (HE-DMT).[2] The indication of treatment for each PwMS is fundamentally determined by clinical and radiological activity, in addition to considering each patient's preferences and the coexistence of comorbidities and social circumstances that may influence the choice of DMT. Moreover, the expectations of the neurologist do not always align with those of the PwMS: the former, are more focused on achieving no evidence of disease activity (NEDA)[3] while PwMS consider other clinical aspects that determine their quality of life (QoL). Many of these factors are often respond poorly to symptomatic treatment and are called "invisible symptoms", including manifestations such as fatigue, depression, spasticity, pain and cognitive impairment. These are very prevalent and pose a significant challenge when treating our patients in clinical practice.

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To achieve better results and optimize treatment in PwMS, we need adequate treatment adherence, making it essential to understand our patients' concerns when proposing a DMT. Lack of adherence leads to therapeutic failure and disease progression,[4] and consequently, increased healthcare costs for health systems.[5] Patient reported outcomes (PROs) provide information directly from patients. These PROs are desirable to better understand their disease, therapeutic preferences and expectations regarding disease progression and treatment. This comprehensive view and the knowledge provided by these questionnaires should be considered when proposing a DMT. Once a DMT is initiated, it is important to assess the degree of satisfaction, not only regarding side effects, but also the perception of efficacy and tolerability.[6]

The integration of PROs into clinical practice allows us to obtain information that we would not otherwise get about the patient's health status and to improve shared decision-making.[7] Treatment satisfaction is one of these variables to be known, in our case through the Treatment Satisfaction Questionnaire for Medication (TSQM), already used in numerous studies in PwMS.[8,9]

Fatigue is defined as the lack of physical and/or mental energy perceived by the individual that interferes with usual activities.[10] It is the most common symptom of the disease, affecting up to 80–90% of patients at any time during its course of their illness[11,12] and impacting QoL.[13–15]

Most DMTs for the relapsing-remitting (RR) form are used long-term, so adherence is a key pillar to obtain the greatest benefit.[16] DMTs are classified based on their efficacy: moderate efficacy (interferon β1-a, interferon β-1b: INF), glatiramer acetate (GA), teriflunomide (TER), dimethyl fumarate (DMF), and high efficacy: fingolimod (FIN), ozanimod (OZA), ponesimod (PON), cladribine (CLAD), natalizumab (NAT), ofatumumab (OFA), ocrelizumab (OCR) and alemtuzumab (ALE).[17] Each of them has a different mechanism of action, mainly aimed at reducing inflammatory activity, decreasing the annualized relapse rate of flares (AAR), the appearance of new lesions or gadolinium enhancement on MRI and the progression of disability.[1,2] The route of administration,[18] treatment satisfaction, side effects and convenience are factors that influence treatment adherence.[5]

There are few published studies that evaluate treatment satisfaction together with DMTs in clinical practice, although there are studies with individual drugs: teriflunomide,[19] fingolimod[20] natalizumab[21] alemtuzumab[22] or cladribine.[23]

The objective of this work is to analyze satisfaction outcomes using the treatment satisfaction questionnaire for medication version 1.4 (TSQM 1.4) based on DMT and its relationship with demographic, clinical and QoL aspects in people PwMS.

Material and Methods

We present a non-interventional cross-sectional study conducted in the demyelinating diseases unit of the Hospital Clínico Universitario San Cecilio. Patients over 18 years old with a diagnosis of RRMS (McDonald 2017) who had been receiving DMT for at least 6 months were invited to participate voluntarily and after informed consent. Demographic, clinical and PRO data (on paper or digitally) were collected between January and June 2024 during scheduled follow-up visits according to usual clinical practice. Exclusion criteria were patients who could not understand or complete the questionnaires according to the physician's criteria and those who had any relapse or progression of disability in the 6 months prior to inclusion.

The variables collected were demographic: age, sex, family history of MS, level of education. Clinical evolution variables (age of onset, evolution time), related to disease activity: disability measure by the Extended Kurtzke Disability Status Scale (EDSS),[24] manual dexterity by the *Nine Hole Peg test* (9HPT),[25] walking speed with the *25-foot walk test* (25FWT).[26] According to the drugs, the DMTs they were receiving, their route of administration, reason for change, number of previous drugs and the last treatment received were noted. Fatigue was determined with the Modified Fatigue Impact Scale (MFIS), a shortened version with 21 items to assess fatigue according to the perception of PwMS in the last 4 weeks, in its physical, cognitive and psychosocial component. Each item is scored from 0 (never) to 4 (almost always), with a maximum global score of 84. The higher the score, the greater the impact of fatigue on PwMS.[27] A score of 38 or more is considered indicative of fatigue.[28] The TSQM. v1.4[29] was used to assess treatment satisfaction. It consists of 14 items that evaluate 4 areas: efficacy, side effects, convenience and global satisfaction. Each domain is coded between 0 and 100, with higher scores indicating greater satisfaction in the subscales. The internal consistency reliability in PwMS is high with Cronbach's $\alpha > 0.90$.[30] Qualitatively, satisfaction with >90 is considered very high, 80–89 high, 65–79

moderate, 40–64 low and <40 very low satisfaction.[29] QoL was measured with the Multiple Sclerosis – Quality of Life-54 (MSQoL-54) questionnaire, generating 12 subscales summarized in physical function and mental function.[31] There is validated Spanish version that t is feasible for administration in Pw MS. The higher the score on the scale, the greater the QoL.[32]

Statistics: Demographic, clinical and PRO characteristics were summarized by mean/median with standard deviation or range for quantitative variables, and number with percentages for qualitative variables. Group analysis was performed using Mann–Whitney U and Kruskal–Wallis tests, while Chi-square and Fisher's exact tests were used for qualitative variables. For linear correlation, Spearman's coefficient (rs) was used. Variables that showed significant differences between groups were considered as potential confounding factors, and a multivariate analysis was applied using quantile regression (quantile 0.5). Statistical significance was considered for *p-values* < 0.05. The software used was SPSS version 28.1.0.1, IBM Corp, Armonk, New York.

Ethical considerations and confidential data treatment: All participants completed written informed consent to participate in this project. Participation was voluntary. All records have been coded to ensure compliance with the Organic Law on Data Protection (Law 15/1999). Data were collected by healthcare professionals from the unit. The project was approved by the Biomedical Research Ethics Committee of Granada with code 1048-N-22 on 3/11/2023 and performed in accordance with the 1964 helsinki Declaration and its later amendments. Also, written informed consent from all participants was obtained after the description of the aim of the study and methods before participation in the study.

Results

A total of 109 people with RRMS were included. The female/male ratio was 2.4 with 70.6% women. 10.3% had primary education, 12.1% secondary education, 21.5% high school and 56.1% higher education. The mean age was 44.4 years for women and 42.2 years for men (p=0.288). The age of disease onset was 34.9 years in women compared to 31.1 years in men (p=0.073). The mean follow-up fo4 PwMS was 10.6 years (SD=8.5) and the mean duration of DMT exposure was 90.2 months (SD=94.1). The mean EDSS was 2.1 points (SD=1.6). The mean 25FWT was 6.82 seconds (SD=3.2) and the dominant hand 9HPT was 24.1 seconds (SD=7.9). There were no differences in DMTs between men and women (p=0.915). 70.2% of PwMS had fatigue, with a higher percentage in women (75.3% vs 58.1%), but without significant difference (p=0.102). There were differences between the group of PwMS taking ME-DMT versus HE-DMT in EDSS, treatment duration, number of previous treatments, reason for change and route of administration. There was no correlation between fatigue and DMT efficacy (p=0.844). The cognitive subscale scored higher in the ME-DMT group and the psychosocial subscale scored higher in the HE-DMT group. PwMS treated with HE-DMT had lower quality of life scores (MSQol-54). Table 1 summarizes the demographics, clinical and PRO results for fatigue and QoL.

In Table 2, we shows the distribution of DMTs in PwMS based on efficacy and route of administration. For 42% of PwMS, the current DMT was the first one they took (naive). Previously 63 patients had been treated with some DMT, of

Table 1 This Table Compares Demographic and Clinical Characteristics Between the Moderate and High Efficacy Groups

	Total n = 109	**Moderate Efficacy n = 48**	**High Efficacy n = 61**	**p value**
Age: mean (SD). years	43.8 (10.9)	43.7 (11.9)	43.8 (9.9)	0.809
Women. n (%)	77 (70.6)	34 (44.2)	43 (55.8)	0.570
Age at diagnosis: mean (SD) years	33.8(9.7)	34.5 (10.3)	33.6 (9.3)	0.755
Disease duration: mean (SD) years	10.6(8.5)	10.7 (9.1)	10.5 (8.0)	0.725

(*Continued*)

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Table 1 (Continued).

	Total n = 109	**Moderate Efficacy n = 48**	**High Efficacy n = 61**	**p value**
EDSS, median (min-max)	2 (0–6.5)	1 (0–5)	2.5 (0–6.5)	<0.001*
Time on treatment mean (DE) months	90.2(94.1)	128 (109)	60.4 (66.6)	<0.001*
Treatment according efficacy n (%) Moderate High	 48 (44%) 61 (56%)	 48 (44%)	 61 (56%)	
Previous treatment count median (min-max)	1 (0–4)	1 (0–4)	0 (0–2)	<0.001*
Reason for change n (%) Naive Side effects Lack of efficacy	 46 (42.2) 16 (14.7) 47 (43.1)	 29 (60.4) 13 (27.1) 6 (12.5)	 17 (27.9) 3 (4.9) 41 (67.2)	<0.001*
Route of administration n (%) Injectable Oral Infusion	 35 (32.1) 51 (46.8) 23 (21.1)	 17 (35.4) 31 (64.6)	 18 (29.5) 20 (32.8) 23 (37.7)	<0.001*
MFIS: n = 104 Mean (SD)	55.9 (21.3)	57.1 (22.3)	55 (20.6)	0.844
MFIS-Physical	24.2 (10)	25.1 (10)	23.5 (9.7)	0.529
MFIS-cognitive	23.6 (10.5)	26.9 (10.4)	21.1 (9.9)	0.012*
MFIS-psychosocial	7.7 (4.6)	5.1 (2.4)	9.9 (4.9)	<0.001*
MSQoL-54 n = 95 Mean (SD)				
MSQoL-physical	52.4 (18.3)	57.3 (16.4)	48.9 (18.9)	0.032*
MSQoL-mental	52 (19.9)	51.5 (18)	53.9 (21.3)	0.530

Notes: Mann–Whitney tests were used for continuous variables and chi-square tests for categorical variables. p-values indicate the statistical significance of the observed differences, p values < 0.05*.
Abbreviations: EDSS, Expanded Disability Status Scale; MFIS, Modified Fatigue Impact Scale; MSQoL, Multiple Sclerosis Quality of Life.

which 47 patients (74.6%) changed drug due to suboptimal response to the previous treatment and 16 patients (25.4%) changed due to side effects. Prior to the current DMT, 82.5% came from moderate efficacy (33.3% from INF, 20.6% from GA, 23.8% from DMF and 4.8% from TER) and 17.5% from high efficacy (7.9% from FIN, 4.8% from CLAD and 4.8% from NAT). Naïve patients compared to those who had changed DMTs showed no significant differences in the TSQM.

Age is related to greater disability measured by the EDSS *(rs* = 0.427 p<0.001) and fatigue measured by MFIS *(rs* = 0.301 p=0.002). The relationship between age and treatment satisfaction measured by TSQM-global *(rs* = - 0.258 p=0.007), TSQM-efficacy *(rs* = −0.344 p<0.001) and TSQM-convenience: *(rs* = −0.198 p=0.039) has been low, and with TSQM-side effects was not significant *(rs* = −0.055 p=0.568). EDSS does not influence the scores of TSQM-global, efficacy and side effect, but it had a weak correlation with lower score in TSQM-convenience *(rs* = - 0.198, p = 0.039). Disease duration and the duration of current DMT treatment are not related to satisfaction in TSQM-global *(rs* −0.062 p = 0.519), nor whit the subscales TSQM-efficacy *(rs* = −0.080 p = 0.408), TSQM-side effects *(rs* = −0.066 p = 0.493) or TSQM-convenience *(rs* = −0.046 p = 0.638).

Table 2 This Table Details the Different DMTs Received by PwMS in Number (n) and Percentage (%), the Efficacy, and the Route of Administration of the DMT

DMT	n (%)	Efficacy	Route of administration
Interferon β-1a/β-1b	14 (12.8)	Moderate	Injectable
Glatiramer acetate	3 (2.8)	Moderate	Injectable
Teriflunomide	6 (5)	Moderate	Oral
Dimethyl fumarate	25 (22.9)	Moderate	Oral
S1P (FIN, OZA, PON)	13 (11.9)	High	Oral
Cladribine	7 (6.4)	High	Oral
Natalizumab	9 (8.3)	High	Intravenous
Natalizumab	13 (11.9)	High	Injectable
Ocrelizumab	13 (11.9)	High	Intravenous
Ofatumumab	6 (5.5)	High	Injectable

Abbreviations: DMT, Disease-modifying treatment; S1P, sphingosine-1-phosphate; FIN, fingolimod; OZA, ozanimod; PON, ponesimod.

We find a correlation between TSQM-global and MFIS (−.0345 rs $p < 0.001$) and between TSQM-global and physical MFIS (−0.305 rs $p = 0.002$), between TSQM-global and cognitive MFIS (−0.404 rs $p < 0.001$) but not between TSQM global and psychosocial MFIS (−0.134 rs $p = 0.175$).

Older age is associated with worse QoL in the physical function score of MSQoL *(rs* = −0.379: $p < 0.001$) but not with mental function ($p = 0.104$).

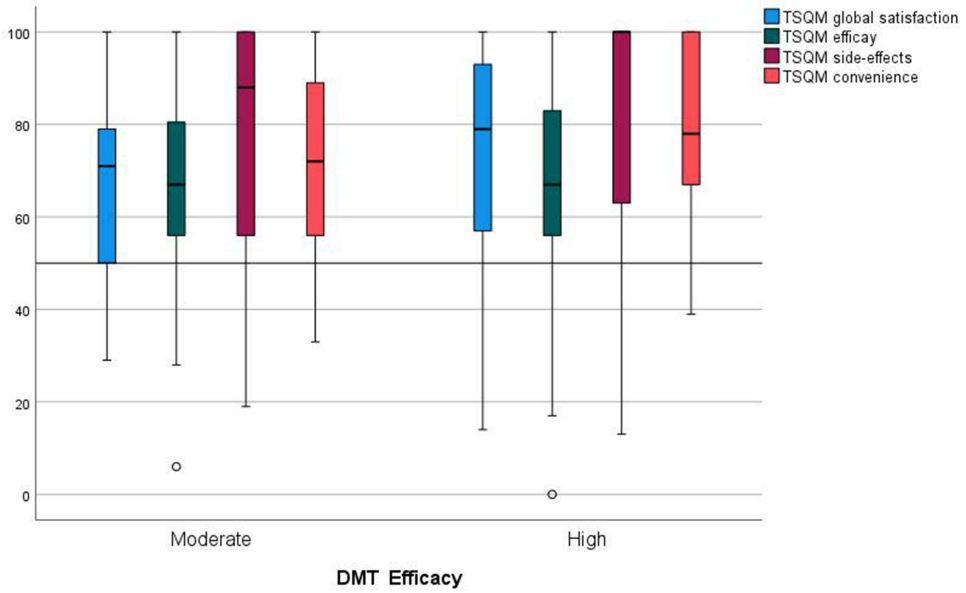

Figure 1 The figure shows box plots comparing TSQM scores for different aspects of satisfaction (global satisfaction, efficacy, side effects and convenience) with two levels of DMT efficacy (moderate and high). Significant differences were determined using the Mann–Whitney test, with $p < 0.05$. Significance was found only in TSQM global satisfaction (blue box) with $p < 0.023$.

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Treatment Efficacy and Satisfaction Level

One objective was to assess treatment satisfaction measured by TSQM based on DMT efficacy. We see that people receiving highly effective DMT (HE-DMT) achieve better TSQM scores compared to those receiving moderately effective DMT (ME-DMT) (Figure 1). The global satisfaction scores obtained in people treated with HE-DMT are higher 75.1 vs 67.2 (p=0.023). Although the results of the other TSQM subscales are better in HE-DMT group, they do not reach statistical significance (Table 3).

A quantile regression model (q = 0.5) was performed to see the influence of EDSS, months of treatment, cognitive MFIS score, psychosocial MFIS score, MSQol-54 quality of life (physical and mental) and treatment efficacy on TSQM global satisfaction scores, as this was the one that achieved statistical significance. HE-DMT is a significant predictor of global satisfaction in TSQM (p = 0.039) increasing global satisfaction by an average of 13.4 units. Meanwhile the physical function of MSQoL has a minimal impact, with an increasing of one unit in global satisfaction increasing the physical function of MSQoL by 0.747 points (p = 0.009). EDSS, treatment duration, and scores in cognitive MFIS, psychosocial MFIS and mental function of MSQoL are not significant predictors in this model (Table 4).

According to the TSQM results we can classify treatment satisfaction as: very low satisfaction (<40 points), low (40–64), moderate (65–79), high (80–89) and very high (90–100). There are statistically significant differences in TSQM global satisfaction, with a higher number of PwMS with very high satisfaction among those treated with HE-DMT and higher number of PwMS with scores between 65 and 79 receiving ME-DMT (p = 0.037). In TSQM-side effects there are

Table 3 Comparison of the Subscales of the Treatment Satisfaction Questionnaire for Medication (TSQM) Between the Moderate and High Efficacy Groups

	Total. n = 109 Mean (95% IC)	**ME-DMT n = 48 Mean (95% IC)**	**HE-DMT n = 61 Mean (95% IC)**	**p-value**
TSQM global	71.6 (67.8–75.4)	67.2 (62.2–72.3)	75.1 (69.7–80.5)	0.023*
TSQM efficacy	67.4 (63.3–71.4)	66.8 (61.3–72.4)	67.8 (61.8–73.8)	0.622
TSQM side effects	79.9 (75.1–84.9)	76.7 (68.9–84.5)	82.5 (76.1–88.9)	0.104
TSQM convenience	75.1 (71.5–78.7)	72 (66.3–77.7)	77.5 (72.8–82.3)	0.164

Notes: The mean (95% confidence interval) is represented. Disease-modifying treatment (DMT). Significant differences were determined using the Mann–Whitney test. p values < 0.05* indicate statistically significant difference between the moderate and high efficacy groups.

Table 4 Dependent Variable: Satisfaction Questionnaire for Medication (TSQM) Global Satisfaction

Parameter	**Coefficient**	**Standard error**	**t**	**gl**	**Sig.**	**95% confidence interval**	
						Lower limit	**Upper limit**
(Intersection)	17.764	22.5234	0.789	82	0.433	−27.042	62.571
Duration DMT months	0.015	0.0278	0.540	82	0.591	−0.040	0.070
EDSS	−0.012	1.8794	−0.006	82	0.995	−3.750	3.727
MFIS cognitive	−0.185	0.3033	−0.610	82	0.544	-0.788	0.418
MFIS psychosocial	0.883	0.7245	1.219	82	0.226	-0.558	2.325
MSQoL physical	0.747	0.2796	2.672	82	0.009*	0.191	1.304
MSQoL mental	−0.147	0.1872	−0.787	82	0.433	-0.520	0.225
HE-DMT	13.395	6.3833	2.098	82	0.039*	0.696	26.093

Notes: Model: (intersection), duration of treatment in months. Values presented are coefficient estimates and standard errors from a quantile regression model for the 0.5 quantile (median) of overall treatment satisfaction, $p < 0.05$ was considered statistically significant.
Abbreviations: EDSS, expanded Disability Status Scale; MFIS, modified Fatigue Impact Scale; MSQoL, Multiple Sclerosis Quality of Life; HE-DMT, High efficacy disease-modifying treatment.

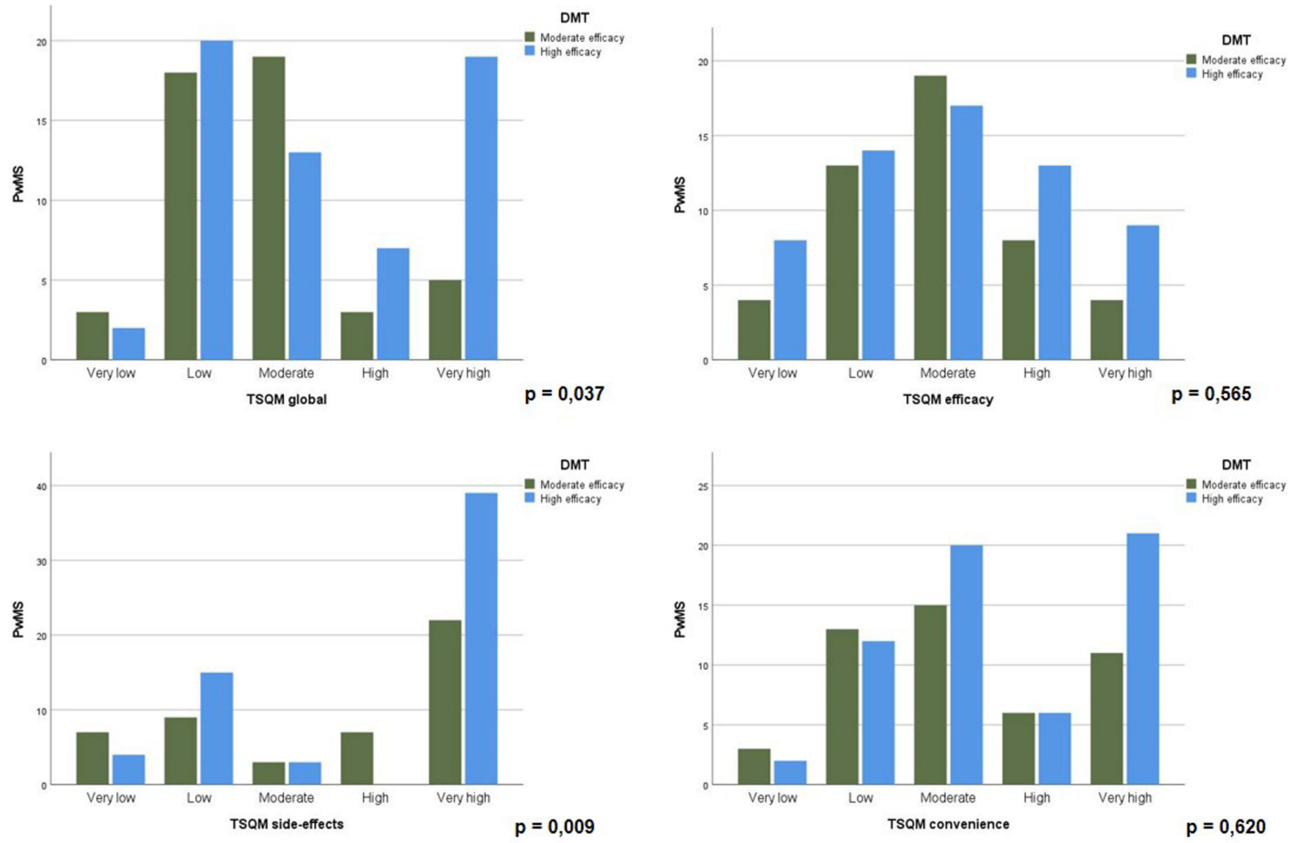

Figure 2 We present the results of Chi-Square and Fisher's Exact for satisfaction scores (TSQM) and DMT efficacy. Multiple comparisons, with Bonferroni correction, revealed significant differences between moderate and very high satisfaction in TSQM global (p=0.040). For TSQM side-effect scores, significant differences were found between the low and high satisfaction groups (p=0.029) and between high and very high satisfaction (p=0.011). No significant differences were observed in TSQM efficacy and convenience between the DMT groups. Statistical significance determined by Fisher's exact test ($p < 0.05$).

better scores in the HE-DMT group (p=0.009). In the TSQM efficacy subscale (p=0.565) and convenience subscale (p=0.620), we did not find a difference (see Figure 2).

If we analyse only the group that had not previously received any DMT (naive patients) which were 46 PwMS and analyze treatment satisfaction when starting with high or moderate efficacy, we obtain better scores in the HE-DMT group: TSQM global 84.5 vs 68.2 points ($p = 0.003$), and TSQM side effects 88.6 vs 75.1 ($p = 0.026$) and TSQM convenience: 84.4 vs 68.6 points ($p = 0.015$). However, no differences were found in TSQM efficacy according to the treatment received: 76.7 vs 68.6 points ($p = 0.101$).

Route of Administration and Treatment Satisfaction

Finally, we wanted to determine if the route of administration influences the perception of DMT satisfaction. The route of administration was infusion therapy in 23 (21.1%), injectable therapy in 35 (32.1%), and oral therapy in 51 (46.8%) of PwMS. The route of administration (injectable, oral or infusion) is not related to treatment satisfaction, sex, age, age of disease onset, or disease duration until our assessment. The duration of DMT exposure varies according to the mode of administration, with the injectable group at 105 months, the oral group at 101 months and the infusion group at 40.8 months ($p = 0.008$). The median EDSS varies in the different DMT groups (injectable, oral and infusion) with 1.5, 1.5 and 4 respectively ($p < 0.001$). The median number of previous treatments was 0.51 for the injectable group, 0.94 for oral and 1.09 for the infusion group ($p = 0.013$). Differences exist in the reason for switching to an oral DMT due to side effects in 87%, while inefficacy was very similar in all three groups (infusions 36.2%, orals 36.1% and 27.7% of cases to an injectable).

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Table 5 The Values Presented are Means and Their 95% Confidence Intervals (95% CI)

	Injectable Mean (95% IC)	Oral Mean (95% IC)	Infusion Mean (95% IC)	p value
TSQM global	73.9 (67.3–80.6)	67.8 (62.2–73.4)	76.6 (67.8–85.4)	0.180
TSQM efficacy	68.6 (60.6–76.5)	64.2 (58.2–70.2)	72.4 (64.3–80.6)	0.305
TSQM side effects	78.8 (69.6–88)	84.7 (78.1–91.2)	71.26 (59–83.5)	0.238
TSQM convenience	71.4 (64.8–78)	78 (72.6–83.4)	74.3 (66–82.5)	0.287
MFIS global	52.3 (45.3–59.4)	59.2 (52.9–65.5)	54.1 (44.4–63.8)	0.403
MSQoL-54				
MSQoL physical	55.6 (49.1–62)	55.3 (50.3–60.4)	42.9 (33.9–51.8)	0.033*
MSQoL mental	56.4 (48.3–63.6)	50.7 (45–56.3)	52.4 (42–62.7)	0.569

Notes: Differences between administration groups were evaluated using the Kruskal–Wallis test. * ($p < 0.05$).
Abbreviations: TSQM, satisfaction questionnaire for medication; MFIS, Modified Fatigue Impact Scale; MSQoL, multiple Sclerosis Quality of Life.

When comparing satisfaction with the route of administration, no statistically significant differences were found between the three groups, although global satisfaction and perceived efficacy are slightly higher with intravenous administration, with oral administration obtaining the best results in the evaluation of side effects and convenience. Analyzing only ME-DMT, we obtain better mean scores in convenience with 77.3 (SD = 18.7) in oral therapy compared to 62.3 (SD = 18) in injectable ($p = 0.015$). In the case of analyzing only the HE-DMTs by oral, injectable and infusion routes, there are no significant differences in TSQM global, efficacy or convenience but there are differences in side effects with a mean of 71.3 vs 89 vs 89.6 in intravenous, oral and injectable respectively (p=0.035), with less satisfaction in TSQM side effects in the intravenous medication group. Pairwise comparisons of TSQM side effects found differences between intravenous vs oral (p=0.029), intravenous vs subcutaneous (p=0.026) and no differences between oral and subcutaneous (p=0.925). There is no difference between the route of administration of previous treatment and satisfaction with the current treatment.

Differences exist in quality of life according to route of administration. Physical function scores of MSQoL were significantly lower in PwMS receiving infusion treatment, 42.9 points compared to 55.6 points for injectables and 55.3 points for oral. No differences were found in the mental function of MSQoL. The presence of fatigue (MFIS) was not related to the route of administration.

Table 5 presents the results of the comparisons of treatment satisfaction questionnaire for medication (TSQM), fatigue (MFIS) and quality of life (MSQoL-54) between different administration modalities.

Discussion

In this non-interventional cross-sectional observational study of real clinical practice, we analyzed treatment satisfaction, quality of life and fatigue outcomes based on the disease-modifying treatment (DMT) used. We also considered demographic and clinical variables that may influence these responses, obtained that patient-reported outcomes (PROs). Shared decision- making between the physician and the patient is fundamental in chronic diseases like multiple sclerosis. This collaborative approach allows for personalized treatment according to the patient's preferences and needs, thereby improving adherence and clinical outcomes.[33]

After analyzing our results, we observed a predominance of women (70%) in our sample, which aligns with the higher prevalence in these groups. The participants` average age was 43 years, similar to that described in other publications related to treatment satisfaction.[9] Having 77% of participants with high school or university education adds robustness to the data obtained through PROs, overcoming the difficulties in their implementation. No age

differences were found between men and women. The age of diagnosis was around 31 years, with no differences by sex and similar to that reported in other studies.[9] The disease duration since diagnosis was approximately 10 years, comparable to the 9.1 years reported in the Australian series.[34] The treatment duration with the drug under evaluation was 90 months, higher than described in other series,[8,9] indicating greater familiarity with DMT and being a reliable source for analyzing satisfaction based on PROs. The EDSS was similar to that found in the natalizumab study by Gold et al[21] and in a German real-life study.[35] However, this figure is somewhat higher than that proposed by Fernandez et al, justified as they focused on moderate-efficacy drugs with lower EDSS.[9] The data provided by Glanz et al are similar to ours, as they include PwMS treated with natalizumab.[8] Although some studies have correlated EDSS with treatment satisfaction as significant, we did not find this relationship in our work, except in the convenience subscale, which showed minimal impact.[9]

The differences observed between highly and moderate-efficacy DMTs are determined by several key factors. High efficacy DMTs are usually employed in more active forms of disease, associated with higher EDSS, and are often administered to patients who have been on treatment longer, usually after having previously received another DMT due to therapeutic failure. The route of administration also varies between both groups. Moderate-efficacy DMTs are mainly administered orally, while high efficacy DMTs predominantly use the intravenous or infusion route. This difference in route of administration is justified by the characteristics of each type of drug. The follow-up time also differs, as ME-DMTs are usually initially employed in less active forms, while HE-DMTs are proposed as an alternative to suboptimal response. It is common for naïve patients vs previously treated patients to differ in follow-up time, similar to most studies of this type.[21] Forty-two per cent of our patients were "naïve" and we found no difference in TSQM scores between these naïve patients and those who had previously received treatment. Most previously treated PwMS switched to HE-DMT due to lack of disease control. When analyzing separately the "naïve" group who received HE-DMT, we obtained significantly better scores on in TSQM global, TSQM side effects and TSQM convenience but no difference in TSQM efficacy.

The prevalence of fatigue was high, around 70%, although similar to that described in other publications.[36] No differences were found between men and women regarding the presence of fatigue. Additionally, fatigue was not related to the DMT. When breaking down the data, we observed that PwMS treated with HE-DMTs had more psychosocial fatigue, while those treated with ME-DMTs had more cognitive fatigue. In a recent study, it was found that ME-DMTs had less fatigue, but this difference did not persist after adjusting for other variables[37] No significant association was found between HE-DMTs and global fatigue. When establishing the relationship between fatigue and treatment satisfaction (TSQM), no previous studies have considered that fatigue may influence responses to the treatment satisfaction survey. However, as we show in our study, that fatigue can act as a confounding factor. Our findings indicate that as fatigue increases, global treatment satisfaction decreases, so it is necessary to know the degree of fatigue when conducting treatment satisfaction studies.

Our data show that PwMS with longer disease duration and higher disability according to EDSS tend to perceive a worse quality of life, especially in the physical subscale of MSQoL-54. This is logical, given that greater physical disability significantly impacts quality of life. Additionally, younger patients better quality of life in the physical subscale *(rs* = −0.379, $p < 0.001$), although this improvement is not observed in the mental function of MSQoL-54.[34]

The distribution of the route of administration of DMTs follows a pattern similar to other studies, with a predominance of the oral route, followed by injectable and finally intravenous.[34] The route of administration is not related to sex, age at onset, or disease duration, consistent with the findings of Hoffmann et al.[35] However, we obtained a higher EDSS in the group treated with infusion.

The treatment satisfaction (TSQM) results in our study were very similar to those of other studies.[5,38] However, they may be somewhat lower than studies that did not include monoclonal DMTs, as these studies do not provide differentiated data between oral and injectable treatments.[17,39]

In our study, the route of administration did not show statistically significant differences in treatment satisfaction scores (TSQM). However, it was observed that global satisfaction and perceived efficacy were slightly higher with the intravenous route. On the other hand, the oral route obtained better scores in the evaluation of side effects and convenience. These results are consistent with published works in terms of treatment efficacy, although they differ in

global satisfaction and convenience. For example, in a prospective study, oral therapy showed a better initial satisfaction level. However, over time, global satisfaction for patients with oral treatment ceased to be significant and did not influence the discontinuation or continuation of the DMT.[34] An Iranian study found that global satisfaction and efficacy rates were higher in injectable DMTs, while convenience was greater in oral treatments, similar to our findings. It is worth noting that this study did not differentiate between infusion and injectable, grouping natalizumab, ocrelizumab and rituximab with interferon and glatiramer acetate under the category of injectable therapies.[40] Although not significant, the differences we obtained in global satisfaction and effectiveness in patients treated with infusion compared to other routes of administration are similar to those obtained in the study by Turčáni et al.[38] If we consider DMTs with INF, GA, DMF, FIN and NAT (injectable, oral and infusion), the results indicate that oral DMTs have greater convenience and present fewer side effects.[41] Although the oral route does not always improve patient satisfaction, as seen when comparing injectable versus infusion natalizumab, where the injectable is preferred for saving time and convenience in administration,[20] there are other factors to consider. According to the meta-analysis by Nicholas et al, although the oral route can improve treatment adherence, specifically with dimethyl fumarate, teriflunomide and fingolimod, it is concluded that approximately one in five patients does not adhere to the oral DMTs studied, and one in four discontinue treatment before one year.[42]

Oral administration could be a factor influencing better quality of life (QoL), according to some publications. Our data suggest that the best QoL scores were observed in patients treated with oral DMTs compared to injectables or infusions. However, the QoL scores were lower compared to other studies (9), which may be attributed to the inclusion of patients with higher EDSS, which are associated with lower QoL. Nevertheless, switching to oral route administration does not always improve QoL, as shown in the work of Stuchiner et al where no difference was found in terms of physical or psychological QoL, without obtaining data on adherence and reasons for changing DMTs.[43] Several authors propose that there are differences in patient satisfaction in favour of oral treatments compared to moderate-efficacy injectables. Higher satisfaction with fingolimod versus moderate-efficacy injectables has been described,[44] and higher satisfaction with teriflunomide compared to INFb-1a.[45] In the no-interventional multicenter study conducted in Germany (CLEVER) with cladribine, an improvement in TSQM scores was observed in all domains, both in patients who switched from oral and injectable medication, with significance in global satisfaction and side effects.[22] In general, QoL and treatment satisfaction results may indicate mechanisms of positive attribution self-amplification. People who experience improvements in QoL and treatment satisfaction may tend to attribute positive outcomes to internal factors, such as the ability to manage their health or a positive attitude.

The scores obtained in the TSQM demonstrate greater global satisfaction with HE-DMTs, regardless of route of administration. Specifically, lower global satisfaction was observed with ME-DMT (67.2 points) compared to HE-DMTs, where the scores were significantly higher (75.1 points). These figures are similar to previous studies, which show comparable scores for ME-DMTs. (9) and higher scores in HE-DMTs.[8] No significant differences were found between drug efficacy and the rest of the TSQM subscales. In our regression model, only high the high efficacy of treatment and, to a lesser extent, the physical quality of life measured by MSQoL, were significant predictors of global satisfaction. Other factors such as EDSS, treatment duration and scores in the cognitive and psychosocial MFIS and mental MSQoL were not significant predictors.

Some authors have determined that the convenience subscale, with lower scores, is associated with lower treatment adherence.[8] Khedr et al in their published series establish that the only predictor of non-adherence to DMT was treatment satisfaction.[36]

There are studies evaluating treatment satisfaction in PwMS,[5,8,9,41] based mainly on differences in the route of administration. However, we have not found publications that study treatment satisfaction based on DMT efficacy grouped into moderate or high efficacy.

Limitations

One of the inherent limitations of open, non-randomized studies without a control group is the risk of selection bias. Being a cross-sectional study, treatment satisfaction data were obtained at a specific time, limiting the ability to establish causal relationships. This approach may affect the generalization of the results and make it difficult to identify changes in

treatment satisfaction over time. The assessment of symptoms through self-reported questionnaires (PROs) may induce response biases from participants. We did not collect data related to switching or dropping out of DMT after the questionnaires were completed, so we cannot correlate whether satisfaction leads to DMT switching. Our sample size is small, although comparable to other similar publications. We cannot establish treatment satisfaction assessments with each DMT individually, as the number of patients treated with each is small, and therefore, the conclusions would not be relevant. We have not analyzed clinical activity of relapses or lesion load on magnetic resonance imaging, which prevents assessing their influence on TSQM results. However, one of the inclusion criteria was clinical stability with no relapses in the last six months, so we believe the influence of these variables would have been minimal and not significant.

Despite these limitations, we consider it interesting to share our results. This study provides novel data on the comparison of moderate and high efficacy disease-modifying treatments in people with multiple sclerosis, something that has not been previously published. Additionally, we have integrated relevant aspects such as fatigue and quality of life, variables that had not been sufficiently considered in previous studies.

Conclusions

Non-adherence to treatment can lead to an increase in clinical and radiological activity, as well as a progressive worsening of disability. Therefore, it is essential to understand patients' preferences in terms of satisfaction, convenience and side effects of the different disease-modifying treatments. Satisfaction with DMT is a key factor influencing treatment adherence.

In our series, the route of administration of disease-modifying treatments did not show differences in TSQM scores overall. However, significant differences were found for moderate-efficacy DMTs, with greater convenience in oral administration. For high-efficacy DMTs, although there were no significant differences between the form of administration and global satisfaction, efficacy or convenience, better scores were obtained regarding side effects in oral and injectable treatments compared to those administered by infusion. We observed that patients receiving HE-DMTs have greater global satisfaction with the treatment. Although the scores in rest of the TSQM subscales are also better in the HE-DMTs group, these differences do not reach statistical significance. We found that treatment efficacy is a significant predictor of global satisfaction. On the other hand, quality of life has a minimal impact on global satisfaction. Other factors, such as EDSS, treatment duration and fatigue (MFIS), were not significant predictors.

Generally, the choice of DMT is based on aspects related to its efficacy and safety. However, due to the diversity of drugs and the different routes of administration available, it is essential to know the experience and satisfaction of PwMS. Conducting PROs is crucial, as it provides valuable information that can help optimize and improve treatment adherence. This knowledge allows healthcare professionals to better understand the preferences and needs of PwMS, adjusting therapeutic strategies the patient experience and maximize treatment effectiveness. This, in turn, contributes to improving clinical outcomes and quality of life for people with multiple sclerosis.

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References

1. Jakimovski D, Bittner S, Zivadinov R, et al. Multiple sclerosis. *Lancet*. 2024;403(10422):183–202. doi:10.1016/S0140-6736(23)01473-3
2. Yang JH, Rempe T, Whitmire N, Dunn-Pirio A, Graves JS. Therapeutic advances in multiple sclerosis. *Front Neurol*. 2022;13:824926. doi:10.3389/fneur.2022.824926
3. Havrdova E, Galetta S, Stefoski D, Comi G. Freedom from disease activity in multiple sclerosis. *Neurology*. 2010;74 Suppl 3:S3–7. doi:10.1212/WNL.0b013e3181dbb51c
4. Steinberg SC, Faris RJ, Chang CF, Chan A, Tankersley MA. Impact of adherence to interferons in the treatment of multiple sclerosis: a non-experimental, retrospective, cohort study. *Clin Drug Invest*. 2010;30(2):89–100. doi:10.2165/11533330-000000000-00000
5. Haase R, Kullmann JS, Ziemssen T. Therapy satisfaction and adherence in patients with relapsing-remitting multiple sclerosis: the THEPA-MS survey. *Ther Adv Neurol Disord*. 2016;9(4):250–263. doi:10.1177/1756285616634247
6. De Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. *Eur J Cardiovasc Nurs*. 2003;2(4):323. doi:10.1016/S1474-5151(03)00091-4
7. Reitzel SB, Lynning M, Skovgaard L. Neurologists' views on patient reported outcomes in multiple sclerosis care. *Heliyon*. 2022;8(6):e09637. doi:10.1016/j.heliyon.2022.e09637
8. Glanz BI, Musallam A, Rintell DJ, Chitnis T, Weiner HL, Healy BC. Treatment Satisfaction in Multiple Sclerosis. *Int J ms Care*. 2014;16(2):68–75. doi:10.7224/1537-2073.2013-021
9. Fernández O, Duran E, Ayuso T, et al. Treatment satisfaction with injectable disease-modifying therapies in patients with relapsing- remitting multiple sclerosis (the STICK study). *PLoS One*. 2017;12(10):e0185766. doi:10.1371/journal.pone.0185766
10. America PV of. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. *Multiple Sclerosis Council Clin Pract Guidelines*. 1998.
11. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. *Mult Scler*. 2006;12(4):367–368. doi:10.1191/135248506ms1373ed
12. Giovannoni G. Multiple sclerosis related fatigue. *J Neurol Neurosurg Psychiatry*. 2006;77(1):2–3. doi:10.1136/jnnp.2005.074948
13. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler*. 2001;7(5):340–344. doi:10.1177/135245850100700511
14. Morales P, Raquel GR, Antonio P, Hernández B, Javier F. Impact of fatigue on quality of life in adults with relapsing remitting multiple sclerosis. *Neurologia*. n.d.;in press.
15. Association of depression in multiple sclerosis with fatigue, sleep disturbances, disability, and health-related quality of life: outcomes of a cross-sectional study n.d. Available from: https://www.elsevier.es/en-revista-neurology-perspectives-17-pdf-S2667049624000383. (Accessed November 18, 2024.).
16. Broadley SA, Barnett MH, Boggild M, et al. A new era in the treatment of multiple sclerosis. *Med J Aust*. 2015;203(3):139–41,141e1. doi:10.5694/mja14.01218
17. Meca-Lallana JE, Martínez Yélamos S, Eichau S, et al. Consensus document of the Spanish Society of Neurology on the treatment of multiple sclerosis and holistic patient management 2023. *Neurología*. 2024;39(2):196–208. doi:10.1016/j.nrl.2023.06.001
18. Thach AV, Brown CM, Herrera V, et al. Associations between treatment satisfaction, medication beliefs, and adherence to disease- modifying therapies in patients with multiple sclerosis. *Int J ms Care*. 2018;20(6):251–259. doi:10.7224/1537-2073.2017-031
19. Hestvik ALK, Frederiksen JL, Nielsen HH, et al. Real- world study of relapsing-remitting multiple sclerosis patients treated with teriflunomide in Nordic countries: quality-Of-Life, efficacy, safety and adherence outcomes. *Mult Scler Relat Disord*. 2022;63:103892. doi:10.1016/j.msard.2022.103892
20. Mitsikostas DD, Orologas A, Dardiotis E, et al. A prospective, observational study assessing effectiveness, safety, and Qol of Greek patients with multiple sclerosis under treatment with fingolimod. *Adv Ther*. 2023;40(5):2217–2233. doi:10.1007/s12325-022-02388-8
21. Gold R, Schmidt S, Deisenhammer F, et al. Real-world evidence and patient preference for subcutaneous versus intravenous natalizumab in the treatment of relapsing-remitting multiple sclerosis - initial results from the observational SISTER study. *Ther Adv Neurol Disord*. 2024;17:17562864241241382. doi:10.1177/17562864241241382
22. Wray S, Jacques F, Miller TA, et al. Satisfaction with alemtuzumab in relapsing multiple sclerosis patients: results from the real-world PRO- ACT study. *Mult Scler J Exp Transl Clin*. 2022;8(4):20552173221135888. doi:10.1177/20552173221135888
23. Ziemssen T, Posevitz-Fejfár A, Chudecka A, et al. Evaluation of therapy satisfaction with cladribine tablets in patients with RMS: final results of the non-interventional study CLEVER. *Mult Scler Relat Disord*. 2024;90:105812. doi:10.1016/j.msard.2024.105812
24. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444–1452. doi:10.1212/wnl.33.11.1444
25. Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler*. 2017;23(5):711–720. doi:10.1177/1352458517690824
26. Kalinowski A, Cutter G, Bozinov N, et al. The timed 25-foot walk in a large cohort of multiple sclerosis patients. *Mult Scler*. 2022;28(2):289–299. doi:10.1177/13524585211017013
27. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis*. 1994;18 Suppl 1(Supplement_1):S79–83. doi:10.1093/clinids/18.supplement_1.s79
28. Flachenecker P, Kümpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler*. 2002;8(6):523–526. doi:10.1191/1352458502ms839oa
29. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the treatment satisfaction questionnaire for medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*. 2004;2(1):12. doi:10.1186/1477-7525-2-12
30. Vermersch P, Hobart J, Dive-Pouletty C, Bozzi S, Hass S, Coyle PK. Measuring treatment satisfaction in MS: is the treatment satisfaction questionnaire for medication fit for purpose? *Mult Scler*. 2017;23(4):604–613. doi:10.1177/1352458516657441
31. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res*. 1995;4(3):187–206. doi:10.1007/BF02260859

32. Aymerich M, Guillamón I, Perkal H, et al. Spanish adaptation of the disease-specific questionnaire MSQOL-54 in multiple sclerosis patients. *Neurologia*. 2006;21(4):181–187.
33. Ubbink DT, Damman OC, de Jong BA. Shared decision-making in patients with multiple sclerosis. *Front Neurol*. 2022;13:1063904. doi:10.3389/fneur.2022.1063904
34. Hardy TA, Parratt J, Beadnall H, et al. Treatment satisfaction in patients with relapsing-remitting multiple sclerosis initiated on teriflunomide in routine clinical practice: Australian observational data. *BMJ Neurol Open*. 2022;4(2):e000315. doi:10.1136/bmjno-2022-000315
35. Hoffmann O, Paul F, Haase R, Kern R, Ziemssen T. Preferences, adherence, and satisfaction: three years of treatment experiences of people with multiple sclerosis. *Patient Preference Adherence*. 2024;18:455–466. doi:10.2147/PPA.S452849
36. Khedr EM, Mahmoud DM, Hussein HB, Malky IEL, Mostafa SS, Gamea A. Treatment satisfaction with disease-modifying therapy is the only predictor of Adherence among multiple sclerosis patients from Upper Egypt. *Sci Rep*. 2024;14(1):7027. doi:10.1038/s41598-024-57116-9
37. Broch L, Flemmen HØ, Simonsen CS, et al. No association between disease modifying treatment and fatigue in multiple sclerosis. *Mult Scler Relat Disord*. 2023;79:104993. doi:10.1016/j.msard.2023.104993
38. Turčáni P, Mašková J, Húska J. Real-world treatment patterns of disease modifying therapy (DMT) for patients with relapse-remitting multiple sclerosis and patient satisfaction with therapy: results of the non-interventional SKARLET study in Slovakia. *PPA*. 2020;14:1129–1135. doi:10.2147/PPA.S254427
39. Saiz A, Mora S, Blanco J. on behalf of the COMPLIANCE study investigators. Therapeutic compliance of first line disease-modifying therapies in patients with multiple sclerosis. *COMPLIANCE Study Neurologia*. 2015;30(4):214–222. doi:10.1016/j.nrl.2013.12.008
40. Molazadeh N, ali SM, Ghajarzadeh M. Disease modifying therapy in multiple sclerosis: evaluation of patients satisfaction in Iranian multiple sclerosis population. *Caspian J Intern Med*. 2023;14(1):89–93. doi:10.22088/cjim.14.1.89
41. Eagle T, Stuart F, Chua AS, et al. Treatment satisfaction across injectable, infusion, and oral disease-modifying therapies for multiple sclerosis. *Mult Scler Relat Disord*. 2017;18:196–201. doi:10.1016/j.msard.2017.10.002
42. Nicholas JA, Edwards NC, Edwards RA, Dellarole A, Grosso M, Phillips AL. Real-world adherence to, and persistence with, once- and twice-daily oral disease-modifying drugs in patients with multiple sclerosis: a systematic review and meta-analysis. *BMC Neurol*. 2020;20(1):281. doi:10.1186/s12883-020-01830-0
43. Stuchiner T, Lucas L, Baraban E, et al. Quality of life among injectable and oral disease-modifying therapy users in the pacific northwest multiple sclerosis registry. *BMC Neurol*. 2020;20(1):439. doi:10.1186/s12883-020-02016-4
44. Fox E, Edwards K, Burch G, et al. Outcomes of switching directly to oral fingolimod from injectable therapies: results of the randomized, open-label, multicenter, evaluate patient outComes (EPOC) study in relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2014;3(5):607–619. doi:10.1016/j.msard.2014.06.005
45. Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled Phase 3 trial. *Mult Scler*. 2014;20(6):705–716. doi:10.1177/1352458513507821