

# Adherence to disease-modifying treatments in patients with multiple sclerosis in Spain

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**Purpose:** Adherence to disease-modifying treatments is essential in order to maximize the beneficial effects of treatment for multiple sclerosis (MS). There are numerous treatments that have been approved. Treatment selection is essential in patient adherence. In addition, patient preference plays an increasingly significant role in treatment decision-making. This study aims to evaluate the degree of adherence, along with other variables that may influence this adherence, in Spain.

**Methods:** A cross-sectional study was conducted with 157 MS patients with disease-modifying treatments. Adherence was assessed using the Morisky Green scale, and other related factors were measured using a questionnaire that addressed demographics, disease characteristics, global perception of pathology, impact of medication on patient's life, and treatment decision-making.

**Results:** The adherence rate was 71% and was associated with the following variables: older age, more treatments received, time to diagnosis 5–10 years, absence of exacerbations, better cognitive status, being married/in a union, clear information about the disease, and higher treatment satisfaction. The main cause for non-compliance was forgetfulness (27%).

**Conclusion:** The adherence rate is acceptable. It is widely known that treatment satisfaction is related to adherence. In our study, patients' level of satisfaction was higher with oral treatments. However, oral administration showed a greater lack of adherence. The main cause of lack of adherence was forgetfulness. In relation to other variables, cognitive status and family support showed a correlation with treatment adherence.

**Keywords:** treatment adherence, oral administration, injectable administration, treatment satisfaction

## Introduction

Multiple sclerosis (MS) is a chronic, unpredictable, degenerative autoimmune inflammatory disease that affects the central nervous system. In general, it begins with an acute inflammatory demyelinating incident followed by new clinical episodes, leading to a diagnosis of relapsing–remitting MS (RRMS). Two-thirds of these patients develop secondary progressive MS (SPMS). In Europe, between 7% (Spain) and 27% (the Netherlands) of cases involve the primary progressive MS (PPMS) form.<sup>2</sup>

MS causes demyelination and axonal damage in the brain and spinal cord,<sup>3,4</sup> which implies a high probability of increasing neurological disability. This is the most common neurological disorder leading to disability in young adulthood,<sup>5</sup> affecting ~2.3 million people worldwide.<sup>6</sup> The most common symptoms of MS exacerbations include paresthesia; motor symptoms; muscle cramping or spasticity; spinal cord symptoms; bladder, bowel, or sexual dysfunction; and fatigue.<sup>7</sup>

To date, MS is still an incurable disease. Treatments are designed to modify the natural evolution of the illness (reducing relapse and disability progression rates)

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with disease-modifying therapies (DMTs) or to alleviate symptoms (reducing inflammation) to improve the patient's quality of life.<sup>7,8</sup>

MS treatment involves a high consumption of health care resources, resulting in significant costs with a high impact on health facilities. In Europe, the annual cost of MS management ranged from €22,800 in mild cases to €57,500 in severe cases.<sup>2</sup> In Spain, this cost was €23,157 and €29,242 in mild and severe cases, respectively, demonstrating elevated costs for the Spanish National Health System. Costs are significantly correlated with disease progression.<sup>9</sup>

Adherence to therapy, especially in chronic cases, is crucial in order for patients to obtain a clinical benefit, although adherence data for other chronic diseases were scarce.<sup>10</sup> Lack of adherence is associated with increased morbidity, mortality, and health care costs.<sup>11</sup> In MS, therapy adherence varies widely (60%–90% with DMTs),<sup>8</sup> and non-adherence has been associated with increased MS-related hospitalizations and relapse rates.<sup>12</sup>

Several factors have been associated with therapy adherence, including age, sex, socioeconomic status, comorbidity, perceived lack of efficacy, MS type, patient attitude, adverse drug effects, forgetfulness, depression, anxiety, and cognitive difficulties.<sup>13,14</sup> Therefore, a better understanding of these factors would increase understanding of MS-treatment adherence, providing useful information for treatment choice. The aim of this study is to evaluate the degree of adherence in MS patients in Spain, and the influence of several variables on this adherence. Secondary aims are to examine patients' satisfaction with their treatment and reasons for changing treatment.

## Materials and methods

### Study design and population

This is a cross-sectional study using a questionnaire to assess adherence to MS treatments. The study was carried out in Spain between June 2017 and September 2017. Data were collected by phone interviews lasting 15–20 minutes.

The study's population consisted of MS patients (with diagnoses of RRMS, SPMS, and PPMS) aged  $\geq 18$  years, who had been receiving pharmacologic treatment for at least 1 year. Considering there are 47,000 MS patients in Spain (based on data from the Spanish Society of Neurology), the calculated sample size was 157, with a sampling error of  $\pm 7.8\%$  at a 95.5% confidence level. Patients were recruited at hospitals and patients associations by health care professionals (physicians and nurses) and patients association staff, who contacted patients and explained the study. This is a

market research that is exempt from approval by a research ethics committee according to Spanish legislation and was conducted in accordance with the EphMRA (European Pharmaceutical Market Research Association) guidelines. Written informed consent was obtained from all patients.

Several variables were controlled for in order to ensure that the sample was representative and to avoid bias. The approximate quotas were set as the following: percentage of MS type according to the known data, current number of treatments, and type of treatment received (ABCR drugs, oral, high-efficacy). In addition,  $< 50\%$  of the sample belonged to patients associations.

### Variables and measurements

The main variable of the study was self-reported adherence to current MS treatments in the previous 6 months, according to the Morisky Green (MG) test.<sup>15</sup> The MG test, validated in the Spanish language,<sup>16</sup> was selected because of its reliability (61%).<sup>15</sup> The degree of treatment adherence was determined by calculating the sum of all correct answers to question P7. The patient was considered as compliant if the answers to the four questions of P7 were: NO/YES/NO/NO (Table 1).

The variables assessed in the study were compiled in a questionnaire, elaborated on and validated by an MS expert committee made up of hospital pharmacists, a neurologist, and professionals, including a nurse from FEMM (Fundación Esclerosis Múltiple Madrid) and a clinical psychologist from EME (Esclerosis Múltiple España). The questionnaire had 57 items structured in seven areas: 1) Sociodemographic and pathology data (12 items); 2) MS information (four items); 3) Current MS treatment (adherence to current treatment) (13 items); 4) Interruptions of current MS treatment (six items); 5) Adherence to previous treatment (eight items); 6) Profile of patient's attitude (one item); and 7) Patient and pathology characteristics (13 items). The items were graded through metrics, scales (1–10), multiple responses, and categories (Table 1).

### Statistical analysis

Descriptive statistics were used to present both quantitative and qualitative variables. Data were expressed as absolute values and percentages (qualitative variables), and summarized using descriptive statistics, such as the mean and SD (quantitative variables). With regard to missing values: once the interview was carried out, if a participant did not answer a specific question, it was considered as not known/not available in the analysis.

**Table 1** Questionnaire: evaluated variables

<b>I. Sociodemographic and pathology data</b>	<b>Response</b>
F1. Spanish province	
F2. Birth year	
F3. Gender	
F4. MS type	
F5. How long have you been receiving medication to treat your MS?	
F5b. In what year did you start taking medication to treat MS?	
F6. How many treatments have you received since you started taking medication for MS?	
F7. What is the medication you are currently receiving for MS?	
F8. If F6 response $\geq 1$ . What was the medication you received for MS?	
F9. If F6 response $> 2$ . Before this, do you remember what was the medication you received for MS?	
F10. Do you belong to any patients association?	
F10b. Which?	
<b>2. MS information</b>	<b>Response (scale 1–10)</b>
P1. To what extent do you consider medication for MS important? Rate with a grade from 1 to 10, where 1 is “Not at all important” and 10 “Very important”	
P2. To what extent do you consider it important to correctly follow the indications about taking your medication for MS? Rate with a grade from 1 to 10, where 1 is “Not at all important” and 10 “Very important”	
P3. To what extent do you think that the INFORMATION that you have received from health professionals about the treatment of MS has been sufficiently CLEAR enough? Rate with a grade from 1 to 10, where 1 is “Not at all clear” and 10 “Very clear”	
P4. Rate with a grade from 1 to 10, where 1 is “I do not care about anything” and 10 “I’m very worried” To what extent do you worry about the following aspects of your medication for MS? <ul style="list-style-type: none"> <li>• Possible mild side effects</li> <li>• Possible serious side effects</li> <li>• (If <math>&gt; 45</math>, do not ask) the possible interference with pregnancy</li> <li>• The way to take/administer the medication</li> <li>• The slowness in its effect/benefit</li> <li>• The impact of medication on your daily life</li> </ul>	
<b>3. Current MS treatment (adherence to current treatment)</b>	<b>Response</b>
P5. What is the name of the medication you are currently receiving for MS?	
P6. How long have you been taking your current medication?	
P7. (Morisky–Green test) Next, focus on the last 6 months and on the medication you are currently receiving for MS. <ul style="list-style-type: none"> <li>• 1= Do you ever forget to take medications to treat your illness?</li> <li>• 2= Do you take the medications at the indicated times?</li> <li>• 3= When you are well, do you stop taking the medication?</li> <li>• 4= If you ever feel bad, do you stop taking it?</li> </ul>	
P7b. If response P7_2=2. Why?	
P8. If response P7_1=1. Have you forgotten any dose in the last 30 days?	
P9. If response P7_1=1. What do you do when you forget a shot of your current medication? <ul style="list-style-type: none"> <li>• 1= I do not take it and wait until the next shot</li> <li>• 2= I take it the moment I remember</li> <li>• 3= In the next shot, I take two (double the dose)</li> <li>• Other (specify)</li> </ul>	
P10. If response P7_1 or P7_3 or P7_4=1. If you forget or stop taking any dose, do you communicate it to your ...? <ul style="list-style-type: none"> <li>• Doctor</li> <li>• Nurse</li> <li>• Hospital pharmacist</li> <li>• Other (specify)</li> </ul>	

(Continued)

Table 1 (Continued)

3. Current MS treatment (adherence to current treatment)	Response
P11. If response P7_2=2. If you do not take the medication at the indicated times, do you communicate it to your ...? <ul style="list-style-type: none"> <li>• Doctor</li> <li>• Nurse</li> <li>• Hospital pharmacist</li> <li>• Other (specify)</li> </ul>	
P12. If response P7_1=1. Why do you think you forget your medication for MS?	
P13. Have you voluntarily stopped taking any dose in the last 30 days?	
P14. For what reasons have you voluntarily stopped taking your medication for MS?	
P15. To what extent do you feel satisfied with the form of your medication (knowing that the majority of the medication can be oral, injectable, intravenous, and is administered daily, weekly, or monthly)?	
P16. If response P15 value is 0-7. Why do you value it in this way?	
4. Interruptions to the current MS treatment	Response
P18. Have you interrupted the medication on any occasion in the last 6 months? <ul style="list-style-type: none"> <li>• 1= Yes, I am not currently taking it</li> <li>• 2= Yes, there was a season that I stopped taking it</li> <li>• 3= No, I have always taken it</li> </ul>	
P19. If response P18=1 or 2. In the last 6 months, how many times have you interrupted the current medication?	
P20. If response P18=1 or 2. For what reasons did you interrupt the medication? <ul style="list-style-type: none"> <li>• 1= I went traveling</li> <li>• 2= I was sick</li> <li>• 3= I had to take another medication</li> <li>• 4= It made me feel bad (side effects)</li> <li>• 5= I wanted to get pregnant/I was pregnant</li> <li>• 6= I did not want to inject myself</li> <li>• Other (specify)</li> </ul>	
P21. If response P18=1 or 2. For how many days did you interrupt treatment the last time you interrupted?	
P22. If response P18=1 or 2. Who made the decision? <ul style="list-style-type: none"> <li>• 1= Own decision</li> <li>• 2= Doctor's decision</li> <li>• 3= Another person (who:)</li> </ul>	
P23. If response P22=1. You reported this interruption to a ... <ul style="list-style-type: none"> <li>• Doctor</li> <li>• Hospital pharmacist</li> <li>• Nurse</li> </ul>	
5. Adherence level to previous treatment	Response
P24. Before the current treatment, did you receive another treatment for MS? <ul style="list-style-type: none"> <li>• 1= Yes</li> <li>• 2= No</li> </ul>	
P25. What medication did you receive before the current one?	
P26. How long did you take it?	
P27. Who decided to change to current medication? <ul style="list-style-type: none"> <li>• 1= Doctor</li> <li>• 2= Patient</li> <li>• Other (specify)</li> </ul>	
P27b. If response P27=1. Why did your doctor change you to the current medication?	
P27c. If response P27=2. Why did you decide to change to the current medication? <ul style="list-style-type: none"> <li>• 1= I wanted to get pregnant/I was pregnant</li> <li>• 2= It was very uncomfortable to take (many pills, I do not like punctures ...)</li> <li>• 3= I never remembered to take it</li> <li>• 4= Because it had no effect</li> <li>• 5= Because it made me feel bad (side effects)</li> <li>• Other (specify)</li> </ul>	

(Continued)

Table 1 (Continued)

5. Adherence level to previous treatment	Response
P28. With what do you think you are more adherent? <ul style="list-style-type: none"> <li>• 1= Current</li> <li>• 2= Previous</li> </ul>	
P29. Why? <ul style="list-style-type: none"> <li>• 1= Administration frequency</li> <li>• 2= Administration route</li> <li>• Other (specify)</li> </ul>	
6. Patient attitudinal profile	Response
P30. There are 3 patient profiles. You may identify with some aspects of the three, but I need you to tell me, with which of the three do you feel more identified with today in relation to MS disease and its treatments? If you had to choose only one? <ul style="list-style-type: none"> <li>• 1= I feel that I can continue living the life that I want and although sometimes I have to adapt to this situation, I can find a way to do it since I am a practical person. My attitude toward illness and treatment is proactive, realistic, and open to new options</li> <li>• 2= Sometimes I feel that neither the doctors nor my family understand what I'm going through. As far as my illness is concerned, I feel alone and not very optimistic in the evolution of the disease and the help that the treatments can provide me</li> <li>• 3= I have learned to live day by day since nobody knows what can happen tomorrow. Adaptability and pragmatism are my main values. "Carpe diem" is a philosophy of life. I try to disconnect from the disease and the treatment by showing an open attitude, without worrying too much, and adapting to things as they come</li> </ul>	
7. Patient and pathology characteristics	Response
P31. In what year were you diagnosed with MS?	
P32. Have you suffered any exacerbation in the last year? <ul style="list-style-type: none"> <li>• 1= Yes</li> <li>• 2= No</li> </ul>	
P33. If response P32=1. How many exacerbations have you had in the last year?	
P34. How many months have passed since you had the last exacerbation?	
P35. How many months have passed between the last exacerbation and the previous one?	
P36. In the last year, how many hospital admissions do you remember were caused by your MS?	
P37. Do you have any impairment/disability caused by MS? <ul style="list-style-type: none"> <li>• 1= Yes → What? _____</li> <li>• 2= No</li> </ul>	
P38. Would you mind telling me what your marital status is? <ul style="list-style-type: none"> <li>• 1= Single</li> <li>• 2= Married</li> <li>• 3= Divorced</li> <li>• Widow(er)</li> </ul>	
P39. Do you need your family's help or outside help for your day-to-day life? <ul style="list-style-type: none"> <li>• 1= Yes → What? _____</li> <li>• 2= No</li> </ul>	
P40. What other health problems do you have besides MS? <ul style="list-style-type: none"> <li>• 1= Hypertension</li> <li>• 2= High cholesterol</li> <li>• 3= Diabetes mellitus</li> <li>• 4= Renal problems (acute/chronic renal failure, lithiasis ...)</li> <li>• 5= Cardiac problems (acute myocardial infarction, heart failure ...)</li> <li>• 6= Respiratory problems (asthma, chronic bronchitis, lung edema ...)</li> <li>• 7= Urologic problems</li> <li>• Other (specify)</li> <li>• No more</li> </ul>	
P41. Should you take other medications to control these problems? <ul style="list-style-type: none"> <li>• 1= Hypertension</li> <li>• 2= High cholesterol</li> </ul>	

(Continued)

**Table 1** (Continued)

7. Patient and pathology characteristics	Response
<ul style="list-style-type: none"> <li>• 3= Diabetes mellitus</li> <li>• 4= Renal problems</li> <li>• 5= Cardiac problems</li> <li>• 6= Respiratory problems</li> <li>• 7= Urologic problems</li> <li>• Other</li> </ul>	
P42. From a scale of 1 to 10, to what extent do you comply with what is indicated by the doctor when taking these other medications?	
P43. What is your employment status? <ul style="list-style-type: none"> <li>• 1= Employed</li> <li>• 2= Unemployed</li> </ul>	

**Abbreviation:** MS, multiple sclerosis.

The minimum level of significance was set at  $P < 0.05$ . BarbWin version 7 (Tesi S.L., Spain) was used for obtaining the distributions (in absolutes and percentages) and the different statistics (mean and SD). IBM SPSS Statistics version 23 (SPSS Inc., Chicago, IL, USA) was used to conduct the significant tests: Student's *t*-distribution (mean) and chi-square (percentages).

## Results

There were 163 patients who agreed to participate in the investigation. Of these, 157 adult MS patients who had been treated for  $\geq 1$  year and were evenly distributed throughout all regions in Spain, met all the criteria to complete the survey and were included in the study (Table 2).

### Sociodemographic characteristics

The mean age of patients included in the study was 43.9 years (SD  $\pm 10.9$ ), and 72% were women. The study population quotas were the following: MS type (RRMS, 75%; SPMS, 18%; and PPMS, 7%), line of treatment (first-line, 58%; second-line, 29%; and third-line, 14%), treatment type (ABCR, 47%; oral, 38%; and high-efficacy, 15%), and membership in patients associations (yes, 47% and no, 53%). The patients' sociodemographic characteristics are summarized in Table 2.

### Disease characteristics

The most common MS type was RRMS, followed by SPMS and PPMS. The mean time to diagnosis was 10.1 years, and 45% of patients had a diagnosis in  $> 10$  years. The mean treatment duration was 8.8 years. Forty-eight percent of patients remained in their first treatment, 31% in their second, and 21% in their third or later treatment. During the last year, only 11% of patients were hospitalized due to MS.

The mean duration of a period free of exacerbations was 31 months. In the last year, 31% of patients had exacerbations: 1 (70%), 2 (22%), and  $\geq 3$  (8%), with a mean time of 18 months since the previous exacerbation.

MS-related symptoms/impairments were reported by 72% of patients; 71% of them with mobility impairment. Other symptoms included: fatigue or loss of strength (29%);

**Table 2** Sociodemographic characteristics of MS patients

Variables (n=157)	n	%
<b>Localization in Spain</b>		
North	28	18
North East	34	22
Center	35	22
East	28	18
South	32	20
<b>Age (years)</b>		
<40	60	38
40–49	52	33
>50	45	29
<b>Gender</b>		
Male	44	28
Female	113	72
<b>Marital status</b>		
Married	90	57
Single	52	33
Divorced	10	6
Widow(er)	4	3
Nk/Na	1	1
<b>Employment status</b>		
Employed	56	36
Unemployed	101	64
<b>Localization</b>		
Urban area	99	63
Rural area	58	37
<b>Patients associations</b>		
Yes	74	47
No	83	53

**Abbreviations:** MS, multiple sclerosis; Nk/Na, not known/not available.



visual, hearing, or vocal impairments (20%); lack of sensibility or cramps (20%); genitourinary impairments (7%); and cognitive impairments (7%). Help from third parties was required by 42% of patients, mainly for household chores (41%) and assistance in moving (29%).

Fifty-four percent of patients reported no comorbidities. Among the remaining patients who mentioned other health problems, 11% reported hypercholesterolemia, 10% urologic disorders, and 8% hypertension. Compliance with comorbidities treatment as reported by patients was high (mean: 8.9/10).

## Current MS treatment and its impact

Current MS treatment in most patients was by injections (62%: 26% intravenous [IV] and 74% subcutaneous [SC], vs oral treatment [38%]). The current mean duration of treatment ranged between 14.2 and 96.7 months: oral (21.6–44.0 months, with less time in use) and injectable (14.2–96.7 months). Patient satisfaction for the type of administration was higher with oral route (mean: 8.6/10) than with injectable treatment (mean: 7.6/10) ( $P<0.05$ ).

Patients' scores (on a scale of 1–10, where 1=not important and 10=very important) for the following aspects of their disease were high: A) medication importance: 9.1; B) importance of following the indications: 9.5; and C) clarity of the information received: 8.8 (where 1=not clear and 10=very clear).

Patients' concerns regarding MS medication were evaluated. Patients considered the possible serious side effects (75%) of medication to be of most concern (scores: 8–10/10). Additional concerns that were not as worrying included; slowness of effect/benefit (59%); the medication's impact on daily life (55%); the form of drug administration (55%); potential interference with pregnancy (51%); and possible mild side effects (47%). With regard to possible mild side effects, patients with IV administration showed a statistically greater concern (72%,  $P<0.05$ ) in comparison with SC (43%) and oral (42%) administration.

## Adherence analysis of current treatment

Adherence was 71%. There were no differences based on the administration route (oral [63%] vs injectable [77%],  $P=0.064$ ). However, in injectable administration, there was greater adherence in patients with IV (100%) than those with SC (68%) ( $P=0.003$ ); Table 3. There was also a significantly greater difference between adherence to IV (100%) and oral (63%) treatment ( $P=0.001$ ).

Among oral treatments, the highest non-compliance rate appeared in patients receiving dimethyl fumarate (65%),

**Table 3** Adherence according to administration route

	Oral (%) (n=59)	Injectable (%) (n=98)		P-value
		IV (%) (n=25)	SC (%) (n=73)	
Compliance	63	77	68	0.064
Forgetfulness	36	100	22	<b>0.003</b>
Patient takes the medication at indicated hours	95	96	30	0.109
Patient does not take the medication if feeling well	0	100	94	<b>0.005</b>
Patient does not take the medication if feeling bad	3	1	1	1.000
		0	1	1.000
		1	1	1.000
		0	1	0.654
		1	1	1.000

**Notes:** Bold values indicate statistical significance.

**Abbreviations:** IV, intravenous; SC, subcutaneous.

followed by fingolimod (29%) and teriflunomide (7%). With regard to injectable drugs, the highest non-compliance rate was observed in patients who were treated with interferon beta-1b (47%), followed by interferon beta-1a (30%) and glatiramer acetate (26%).

There was a statistically significant association between treatment adherence and the following variables: older age (mean of 40.4 years in non-compliance patients vs 45.2 years in compliance patients,  $P=0.013$ ); more treatments received; time to diagnosis 5–10 years; better cognitive and memory status; being married/in a union; having received clear information about the treatment; and higher satisfaction with the current administration route (Table 4).

The main cause for non-compliance was forgetfulness (27%), which was found to be significantly associated with SC and oral routes (SC: 30%,  $P=0.005$ ; oral: 36%,  $P=0.005$ ) rather than IV (0%); Table 3. Only 5%, 1%, and 2% of patients stated non-compliance in the remaining MG test items, 2, 3 and 4, respectively.

Among patients who sometimes forgot their medication in the last 6 months, 37% did so during the last month, with higher percentages in oral than injectable medication (43% vs 32%). The reasons for forgetting were the following: absent-mindedness (42%); leisure time (9%); traveling (9%); scheme confusion (7%); lack of foresight (7%); and other (discomfort with carrying it; job; welfare; malaise; and boredom) (18%). Patients' actions after forgetting an intake were the following: waiting until the next intake (51%); taking the medication once they realized it had been forgotten (21%); taking two doses in the next administration (5%); waiting until the next intake if more than 4 hours had passed (5%); other (7%); and not known/no answer (11%).

**Table 4** Adherence to treatment in MS patients

<b>N=157</b>	<b>Compliance (%) (n=112)</b>	<b>Non-compliance (%) (n=45)</b>	<b>P-value</b>
<b>Age (years)</b>			
<40	34	49	0.118
40–49	34	31	0.879
≥50	32	20	0.185
Mean	45.2	40.4	<b>0.013</b>
<b>Gender</b>			
Male	27	31	0.727
Female	73	69	0.727
<b>MS type</b>			
RRMS	72	80	0.426
SPMS	21	13	0.410
PPMS	7	7	1.000
<b>Number of treatments</b>			
Mean	2.0	1.6	<b>0.046</b>
<b>Patients associations</b>			
Yes	46	49	0.918
No	54	51	0.918
<b>Diagnosis (years)</b>			
<5	19	38	<b>0.021</b>
5–10	36	18	<b>0.035</b>
>10	45	44	1.000
Mean	10.7	8.9	0.152
<b>Exacerbation incidence focused on the last year</b>			
Exacerbations	30	33	0.862
No exacerbations	70	67	0.862
Exacerbations (mean)	1.6	1.3	0.474
<b>Exacerbation incidence</b>			
Months since last exacerbation (mean)	32.9	27.0	0.329
<b>Affectation/disability due to MS</b>			
With affectation/disability	72	71	1.000
Without affectation/disability	28	27	1.000
Nk/Na	0	2	1.000
<b>Cognitive affectation due to MS</b>			
Cognitive affectation	3	19	<b>0.002</b>
Memory loss	1	16	<b>0.002</b>
<b>Marital status</b>			
Married	63	42	<b>0.025</b>
Not married	37	58	<b>0.025</b>
<b>Issues associated with medication</b>			
Medication importance (mean)	9.1	9.2	0.713
Importance of following indications (mean)	9.5	9.4	0.569
Clear information (mean)	8.9	8.4	<b>0.028</b>
<b>Current treatment</b>			
Current oral treatment	33	49	0.940
Current injectable treatment	67	51	0.940
Current medication, months (mean)	43.7	56.7	0.100
<b>Satisfaction with the current administration</b>			
Satisfaction with oral treatment (mean)	9.1	8.0	<b>0.016</b>
Satisfaction with injectable treatment (mean)	7.9	6.5	<b>0.011</b>
<b>Patients' profile according to their attitude toward the disease</b>			
Pragmatic	49	60	0.796
Proactive and realistic	35	31	0.359
Unoptimistic	16	9	0.246

**Note:** Bold values indicate statistical significance.

**Abbreviations:** MS, multiple sclerosis; Nk/Na, not known/not available; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.



Fifty-one percent of patients did not express medication forgetfulness. The patients who did communicate this mainly to their doctor (33%: always [86%] and sometimes [14%]), to a nurse professional (23%: always [70%], sometimes [30%]), or to a pharmacist (2%).

Regarding voluntary non-adherence, only 1% of MS patients reported voluntarily stopping the treatment in the last 30 days due to laziness or feeling unwell. Considering a prolonged evaluation period (the last 6 months), 5% of patients reported treatment interruption (71% by a physician's decision; 29% by their own decision [due to other drug administration, or because they felt unwell due to medication]). During this 6-month period, the mean number of interruptions was 1, and the mean duration of treatment was 67.5 days.

### Previous treatment and reasons for change

Fifty-two percent of patients previously received a different type of treatment: oral (10%), injectable (86%: 21% IV and 79% SC), and unknown (4%). The previous mean treatment duration ranged from 26.0 to 122.8 months: oral from 12.0 to 26.0 months, and injectable from 12.0 to 122.8 months.

The persons who initiated the change in medication were the following: the physician (94%); the patient (13%); or the nurse (1%). The reasons were the following: lack of efficacy/presence of exacerbations (38%); feeling unwell (37%); uncomfortable to take (19%); hepatic problems (6%); virus infection (5%); virus prevention (3%); and other (8%).

### Patient profiles according to their attitude toward the disease

Three attitudinal patient types were reported as the following: pragmatic (52%); proactive and realistic (34%); and unoptimistic (14%). There were no differences in adherence levels between these patient profiles.

## Discussion

This study aims to determine the adherence to treatment of MS patients in Spain, according to the influence of several variables. The adherence rate observed was 71%, slightly higher than that of another Spanish study using the same test (68%)<sup>8</sup> as well as those of additional studies in other countries conducted with MG tests (46%) and Medication Possession Ratio (54%).<sup>17,18</sup>

Regarding the administration route, our results show a higher adherence with injectable forms (77%: 68% SC and 100% IV, vs oral [63%]). In general, the injectable and SC results were considered as falling within acceptable limits, showing a higher percentage than that observed in

another study with oral and self-injectable administrations in MS patients, although this study used another adherence method.<sup>18</sup> It is important to highlight that IV administration is more adherent than SC and oral administrations. This difference could be explained by the different administration schedule for IV treatment, which is less frequent. With regard to this, a study showed that adherence increased in treatments with lower administration frequency.<sup>19</sup> This difference in adherence could also be explained by the fact that the IV route is administered by health care professionals by medical appointment, whereas the SC and oral routes are administered by patients themselves.<sup>19,20</sup> Some hospitals issue reminders for patients to come in for treatment, but we cannot state that this is a homogenous practice in Spain. Therefore, we have concluded that both reasons could be plausible explanations for the difference in adherence.

The main cause reported for non-compliance was forgetfulness. This unintentional behavior has been broadly observed as the main cause of non-adherence in MS patients.<sup>17,21,22</sup> In our study, there was no difference in adherence between SC and oral administration, as another previous study showed.<sup>18</sup> However, both routes were significantly associated with forgetfulness, compared with IV administration. As noted previously, this could be due to a direct relationship between adherence and lower administration frequency,<sup>19,23</sup> or a result of medical reminders for IV treatments.

Several variables were positively associated with adherence: older age; more treatments received; time to diagnosis 5–10 years; better cognitive status; fewer memory problems; being married/in a union; having received clear information about the disease; and higher treatment satisfaction. Despite these variables being associated with adherence, when we assessed attitudinal patient profiles, no differences in adherence were found. Therefore, it is difficult to establish a profile of patient compliance.

With regard to age, it has been noted that younger age is significantly associated with high adherence, but this was based on the number of injections administered in the previous month and interferon beta-1b only.<sup>8</sup> However, other studies have also shown that patients aged  $\geq 45$  years are more likely to be adherent,<sup>24</sup> and there is a positive change in the probability of being adherent as age increases.<sup>24,25</sup> This latest study is in concordance with the result that we observed, which may additionally justify the association of  $< 5$  years of diagnosis with non-compliance, despite several studies associating shorter durations of the disease with greater adherence to treatment.<sup>17,26</sup> On the other hand,

our study showed that higher age was positively associated with adherence, independent of the injectable route (IV or SC). It was not surprising that a better cognitive status over the years was associated with greater adherence. The impact of the cognitive status was corroborated by the poor adherence found in patients with cognitive impairment.<sup>24,27</sup>

Family and social environment are important factors in adherence, and living alone is a factor of non-compliance.<sup>28</sup> Our results show a positive correlation between being married/ in a union and adherence; almost all patients feel extrinsically motivated by their family to adhere to treatment.<sup>17</sup>

Clear information about the disease promotes better adherence, and, therefore, misinformation and lack of understanding of the disease are associated with non-compliance.<sup>27</sup> More information and higher awareness (which could have been acquired during previous treatments) would explain the result in our study of greater adherence being associated with more treatments received. This would also indicate that treatment adherence can be a representative marker of patients' behavior regarding their health.<sup>29</sup> In this sense, our patients with concomitant diseases showed a high level of compliance, indicating that these patients tend to be compliant in general.

Treatment satisfaction was higher in oral administration than in injectable, and both were significantly higher in compliant patients. Several studies have shown that satisfaction is a determinant of adherence<sup>30-32</sup> and is associated with fewer relapses, a longer duration of medication, a lower disability score, and the absence of several side effects.<sup>10</sup> Despite our patients showing high satisfaction with oral administration, adherence to this type of treatment was lower. Satisfaction with injectable administration was also significantly higher in adherent patients, supporting the levels of adherence observed. It is known that the main reasons for lack of satisfaction are treatment inconvenience (needing regular injections can affect acceptance of treatment), injection burden of IV, injectable DMTs, and injection site reactions.<sup>33,34</sup> In this context, our patients who received medication with IV administration showed a statistically higher concern for these possible mild side effects; this was primarily true for young people and women, who also showed higher levels of compliance.

The compliance group was defined as, patients who were older, received more treatments, were diagnosed less than 10 years ago, possessed a better cognitive state, were married/in a union, received clear information about the disease, and showed high levels of satisfaction with the treatment. The compliance group was formed exclusively

by individuals who presented a score of 0 in the MG test, and the non-compliance group was comprised those that scored 1 or higher.

With regard to the current treatment received and its impact, most patients were receiving an injectable treatment. The injectable route continues to be the preferred route and was the first route established with a well-defined and easily treatable adverse effect profile.<sup>33</sup> Other worrying concerns related to treatment found in our study were the following: possible serious side effects, slowness of effect/benefit, the medication's impact on daily life, form of the treatment administration, and potential interference with pregnancy. These concerns have previously been shown in similar populations.<sup>10,33,34</sup>

Although satisfied with their current treatment, 52% of patients previously received a different type of treatment. Reasons to change were mainly related to the treatment itself and not to patient preference. These reasons were the following: inconvenience of the administration regimen; side effects; flu-like symptoms; and lack of efficacy, as shown by other studies.<sup>10,33,35</sup> The change of treatment was initiated by a physician or nurse, although nowadays patient preferences play a major role in treatment decisions.<sup>5</sup> In this sense, convenience of administration and the ease of safety monitoring in the long-term course of oral treatment are essential to patient satisfaction and adherence, showing that satisfaction is a determinant of adherence.<sup>30-32</sup> However, according to our results, patients receiving oral treatment are less adherent. As in other studies, the drug administration frequency and medical reminders for IV treatments most likely play a greater role in adherence.<sup>19,23</sup>

Limitations of this study should be considered when interpreting its findings. Only one method to evaluate adherence was employed. Although this method is widely used, in order to confirm this result, it is necessary to use other methods. Due to the reduced sample size, these results should be treated with caution and considered as a first approach. In addition, the patients who agreed to participate and answer the questionnaire may represent a group of the population that is more actively engaged with their disease, leading to a higher level of adherence being observed in the present study.

## Conclusion

Our study shows an acceptable adherence rate (71%), associating several factors to an adherent patient profile (treatment, disease, and personal characteristics). Patients gave high importance to their disease and showed a reasonable level of satisfaction with their current treatment. Though

satisfaction is related to adherence (and satisfaction was higher with oral treatments), oral administration showed a lower level of adherence. This may be due to the fact that the main cause of lack of adherence in MS patients is forgetfulness, and, therefore, other variables have greater importance, such as cognitive status and family support. A deep understanding of adherence rates is necessary when considering future strategies to improve clinical results and reduce non-pharmacological costs.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper. gave approval of the final version to be published and agree to be accountable for all aspects of the work.

## Disclosure

Raquel Fernández-Del Olmo has disclosed that she is an employee of Roche Farma, S.A. The authors report no other conflicts of interest in this work.

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