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Original article

Therapeutic status quo in patients with relapsing-remitting multiple sclerosis: A sign of poor self-perception of their clinical status?

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ABSTRACT

Background: Status quo (SQ) bias is defined as patient´s tendency to continue taking a previously selected but inferior therapeutic option.
Objective: To assess the presence of SQ bias and its associated factors in patients with relapsing-remitting multiple sclerosis (RRMS).
Methods: A multicenter, non-interventional study involving 211 patients with RRMS was conducted. Participants answered questions regarding risk preferences and management of simulated MS case-scenarios. The SymptoMScreen (SMSS) questionnaire was used to assess the perception of severity from the patients´ perspective. SQ bias was defined as patients' preference to maintain the current treatment despite evidence of disease activity. Mixed linear models adjusting for clustering assessed the association of candidate predictors with the outcome of interest.
Results: The mean age (SD) was 39.1 (9.5) years and 70.6% were women. SQ bias was observed in 74.4% (n = 161) participants. Univariate analysis showed that SMSS score was associated with SQ bias (OR 1.04; 95% CI 1.01-1.07). Mixed linear regression models suggest that for every point increase in SMSS, there was a 4% increase in the likelihood of SQ bias (β 0.04; 95%CI 0.015-0.06; $p < 0.002$). Among the different symptomatic dimensions included in the SMSS, only vision impairment (β 0.32; 95%CI 0.05-0.50) and depression (β 0.29; 95%CI 0.006-0.58) remained associated with SQ bias in the multivariate analysis. There was no association between participants' risk preferences and SQ bias.
Conclusions: Unwillingness to pursue treatments that are more effective is a common phenomenon affecting over 7 out of 10 patients with RRMS. This phenomenon appears to be driven by patients' negative self-perception of their clinical status.

Multiple sclerosis (MS) is a chronic autoimmune neurological disorder with a negative impact on patients, their families, and society (Kobelt et al., 2017; García-Domínguez et al., 2019). In recent years, the approval of several new disease modifying therapies (DMT) with different efficacy-risk profiles has added more complexity to the clinical management of MS (Montalban et al., 2018; Saposnik and Montalban, 2018). In this context, there has been a growing interest in patient's views under the paradigm of patient-centered outcomes (Khurana et al., 2017; D´Amico et al., 2019). Establishing treatment goals together with patients is still an unmet need (Yeandle et al., 2018; Day et al., 2018). Shared decision-making emerged as a potential solution, but is hindered by multiple factors, such as physician-patient communication, knowledge gaps regarding therapeutic alternatives, or subjective patient factors not shared with their MS specialists (O´Conor et al., 2007; Kachuck et al., 2011).

Therapeutic inertia (TI) is defined as physicians' lack of treatment

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initiation or escalation when treatment goals are unmet (e.g. disease activity by accepted clinical and/or radiological parameters) (Saposnik and Montalban, 2018). TI is recognized as an important physician factor leading to suboptimal care in MS in many countries (Saposnik and Montalban, 2018; Almusalam et al., 2019). On the other hand, status quo (SQ) bias is defined as patients´ preference to maintain the current treatment despite clinical and radiological evidence of disease activity (Suri et al., 2013). SQ bias denotes a patient attribute in a similar way as TI is related to physicians. Limited information is available regarding the prevalence of SQ bias and its determinants in patients with MS.

We hypothesized that some individual patient characteristics (e.g. number of relapses in the last year, current disability, subjective perception of symptoms) are associated with SQ bias in MS patients and that SQ bias may be a common phenomenon. In the present study, we evaluated the presence of SQ bias and its associated factors in a population of patients with relapsing-remitting multiple sclerosis (RRMS).

1. Methods

We conducted a non-interventional, cross-sectional study involving patients with RRMS receiving care in 17 MS centers in Spain between December 4, 2018 and March 5, 2019 (PERCEPTIONS-MS study). Key eligibility criteria included age 18 years and older, a diagnosis of RRMS according to the 2010 revised McDonald criteria, and an Expanded Disability Status Scale (EDSS) score range from 0 to 5.0 (Polman et al., 2011; Kurtzke et al., 1983). Written informed consent was obtained from all subjects. The study was approved by the institutional review board of the Hospital Universitari Clínic i Provincial de Barcelona.

1.1. Study flow

Participants first answered questions regarding demographic data and perception of symptom severity. Investigators collected clinical characteristics and assessed patients´ cognition. Patients then watched a segment of a publicly available tutorial about MS diagnosis and treatment (https://youtu.be/m37WzLseWUI). Participants were informed about treatment options, presented as a menu of non-branded hypothetical options (labelled as Treatments A-F) with different efficacy and safety profiles mimicking the currently available disease-modifying agents (Table 1) (Li et al., 2019; Lucchetta et al., 2019). The tutorial and menu of treatment options explained the accepted criteria used by MS specialists to switch or escalate therapies. A case-vignette was used as an example to assess patient understanding of the treatment escalation criteria.

Finally, patients completed behavioral experiments to assess risk preferences and were asked to choose their treatment preference in twelve simulated MS case-scenarios or case-vignettes (eight case-scenarios were focused on SQ bias). Simulated case-scenarios were originally designed by our research team and MS experts (GS, JM, APS, EHML) derived from the most common situations experienced by patients in clinical practice. The study (simulated case-scenarios, treatment options and tutorial) were conducted in Spanish, the mother tongue of patients. Case-scenarios are shown in Appendix. Further details of the study flow are presented in Fig. 1.

The SymptoMScreen (SMSS) questionnaire was used to assess patients' self-perception of symptom severity (Green et al., 2017; Meca-Lallana et al., 2020). Cognitive performance was assessed using the Symbol Digit Modalities Test (SDMT) (Benedict et al., 2017). We evaluated risk preferences by identifying the safe amount for which a participant is indifferent to a 50/50 gamble of winning an amount X or 0 euros against a safe option (Christopoulos et al., 2009; Saposnik et al., 2016). This indifference amount, called certainty equivalent, reflects the participant-specific value associated with the risky option. For example, participants were asked what would be the minimum amount of money that they would prefer obtaining for sure instead of the equiprobable gamble of winning 400 or 0 euros. We also used the German Socio-Economic Panel (SOEP), a validated survey that evaluates willingness to take risks in different domains of daily life (Wagner et al., 2007). Further details of these tests are published elsewhere (Saposnik et al., 2016).

1.2. Outcome measures

SQ bias was defined as patients' preference to maintain the current MS treatment in the simulated case-scenarios (e.g. first-line injectable therapies) despite new clinical relapses and radiological evidence of disease activity. We created a SQ score with the number of case-scenarios that met the criteria for SQ bias over the total number of scenarios presented. SQ bias was also analyzed as a categorical variable dichotomized as SQ bias present vs. absent. A secondary outcome measure included SQ4, defined as SQ bias in 4 or more case-scenarios to assess the consistency of the association with potential covariates.

1.3. Statistical analysis

We used non-parametric tests (Wilcoxon rank-sum and Kruskal-Wallis test) to compare continuous and categorical variables between

Table 1
Hypothetical treatment options

	Efficacy (annualized relapse rate reduction)	Frequent, but mild side effects (20-30%)	Rare, but severe side effects (1-5%)
Treatment A			
SC 3 times a week, or every 2 weeks, or IM weekly	Approximately 30%	Flu-like symptoms, skin reaction at the injection site	Liver injury
Treatment B			
SC 3 times a week	Approximately 30%	Skin reaction at the injection site	Abscess, inflammation of skin/soft tissue underneath
Treatment C			
Once-daily oral	Approximately 30%	Gastrointestinal symptoms	Liver injury
Treatment D			
Twice-daily oral	Approximately 50%	Gastrointestinal symptoms, flushing	Severe infections
Treatment E			
Once-daily oral	Approximately 50%	Slow heart rate (bradycardia)	Severe infections
Treatment F			
IV 5 consecutive days (first year) + 3 consecutive days (second year)	Approximately 80%	Thyroid disorders	Severe infections, autoimmune disorders
Treatment G			
IV monthly	Approximately 80%	-	Severe infections

IM: intramuscular; IV: intravenous; SC: subcutaneous.

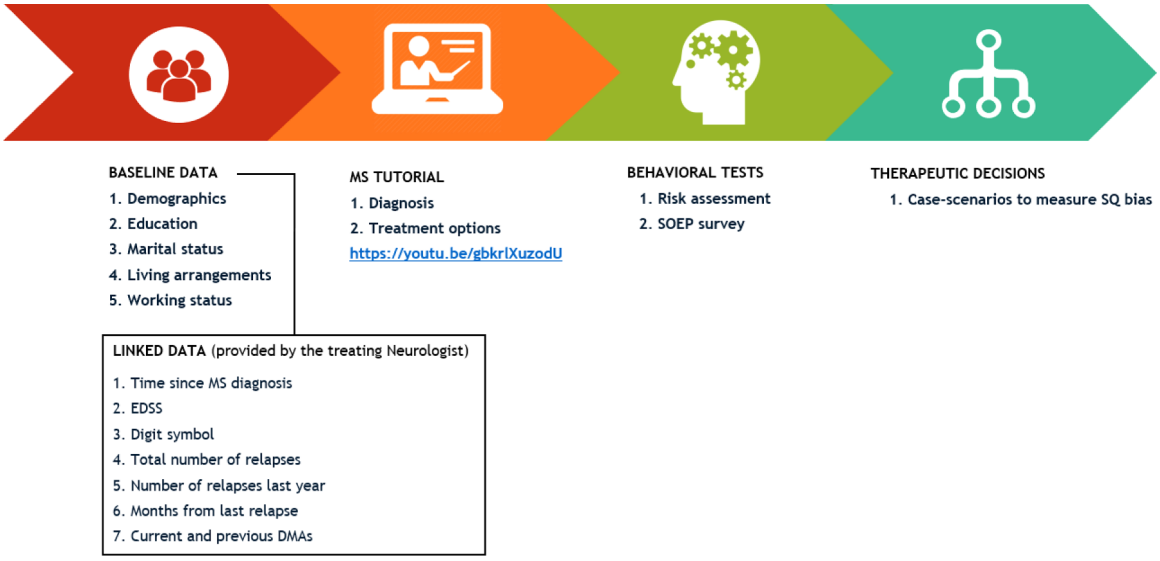


Fig. 1. Study flow
EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SOEP: Socio-economic Panel; SQ: status quo.

groups. SMSS was primarily analyzed as a continuous variable. We also divided SMSS in quartiles (Q1: no symptoms at all to mild symptoms, Q4: severe symptoms) to determine the presence of a gradient effect on the outcomes of interest. Mixed linear models adjusting for clustering assessed the association of candidate predictors with the outcome of interest. Multilevel mixed-effects logistic regression adjusting for clustering assessed the association of candidate predictors with the outcome of interest (SQ bias present vs. absent and SQ4). For multivariate analysis of individual responses, we included a random effect of participant (211 levels) and a random effect of scenario (8 levels), because responses are cross-classified by participant and scenario. The aim of this analysis was to evaluate the contribution of individual-specific variables to the variation of SQ bias. Variables for adjustment were selected a priori based on previous studies on factors influencing treatment decisions, including participant's age, sex, disease duration, total number of relapses, months from last relapse, EDSS score, SMSS score, SMDT score, number of DMT, and risk preferences (Lynd et al., 2016; Visser et al., 2020; Saposnik et al., 2017a; Saposnik et al., 2017b). There was no data imputation.

A sensitivity analysis was conducted by adding living status (alone vs. other- partner or caregiver) and marital status (single, married, other). We also analyzed the depression subscore of the SMSS scale by SQ bias. C-statistics was used to assess discrimination ability of the models, whereas the roccomp command was used to compare differences between regression models after adjustment. All tests were 2-tailed, and p-values <0.05 were considered significant. We used STATA 13 (College Station, TX: StataCorp LP) to conduct all analyses.

2. Results

From a total of 218 participants who met the inclusion criteria, 211 (96.8%) patients completed the study. Completed clinical data as provided by the treating physician was available for 161 (76.3%) participants, whereas in the remaining 50 participants their responses could not be properly matched with objective clinical information reported by their neurologist. The mean age (SD) was 39.1 (9.5) years and 70.6% were women. The main demographic and clinical characteristics of the sample are shown in Table 2.

The mean SMSS score (SD) was 16.5 (14) [(median score: 13, IQR [4-27]).

The mean SQ bias score (SD) was 2.82 (2.0). Overall, SQ bias was present in at least one case-scenario in 74.4% (157/211) of participants.

Table 2
Demographic and clinical characteristics

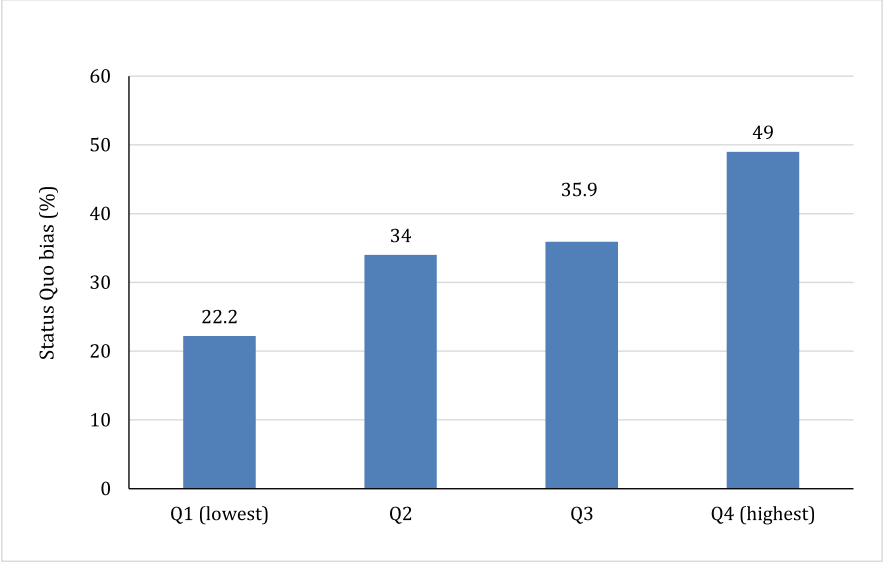
	Total (n = 211)
Age (years), mean ± SD	39.1 ± 9.5
Sex (female), n (%)	148 (70.1%)
Education, n (%)	
Primary	31 (14.7)
Secondary	74 (35.1)
Tertiary	106 (50.2)
Living status, n (%)	
Alone	27 (12.8)
With a partner	122 (57.8)
With family members	55 (26.1)
Other	7 (33)
Time since diagnosis (years), mean ± SD	6.64 ± 4.45
Number of relapses since diagnosis, mean ± SD	3.5 ± 3.7
Number of relapses in the last year, mean ± SD	0.4 ± 0.7
Number of DMTs since diagnosis, mean ± SD	2.13 ± 1.16
EDSS median (interquartile range)	2.0 (1.0-2.5)
SDMT score, mean ± SD	52.2 ± 20.5
Risk preference, mean ± SD	246.0 ± 107
SOEP, mean ± SD	28.3 ± 14.5
SymptomMScreen score, mean ± SD	16.5 ± 13.9

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SDMT: Symbol Digit Modalities Test; SOEP: Socio-economic Panel; SD: standard deviation; SQ: status quo.

Thirty-five percent (n = 74) of participants were unwilling to switch therapy in half or more of the presented scenarios (SQ4) despite being informed of the high risk of disease progression. The analysis of individual responses showed that 614/2110 (29.1%) met the SQ bias criteria. There was a higher number of individual responses meeting the SQ criteria for patients with higher SMSS scores (p-value: 0.02). The distribution of SQ bias by quartiles of SMSS groups is shown in Fig. 2 (Panel A). There was no association between prior exposure to DMT and SQ bias (Fig. 2, panel B). There was also no association between participants' risk preference and SOEP with SQ bias (p-values of 0.44 and 0.51, respectively). There were no significant differences in cognitive function (mean SDMT 51.4 vs 54.5; p = 0.38) and depression (10.2% vs. 5.6%; p = 0.31) between participants with and without SQ bias.

The univariate analysis showed that SMSS score was associated with SQ bias (unadjusted OR 1.05; 95% CI 1.02-1.07). Similar findings were observed after adjustment for age, sex, education, living status, disease duration, total number of relapses, EDSS score, and number of previous

Panel A. SQ by quartiles of SMSS symptoms



Panel B. SQ by previous exposure to DMT

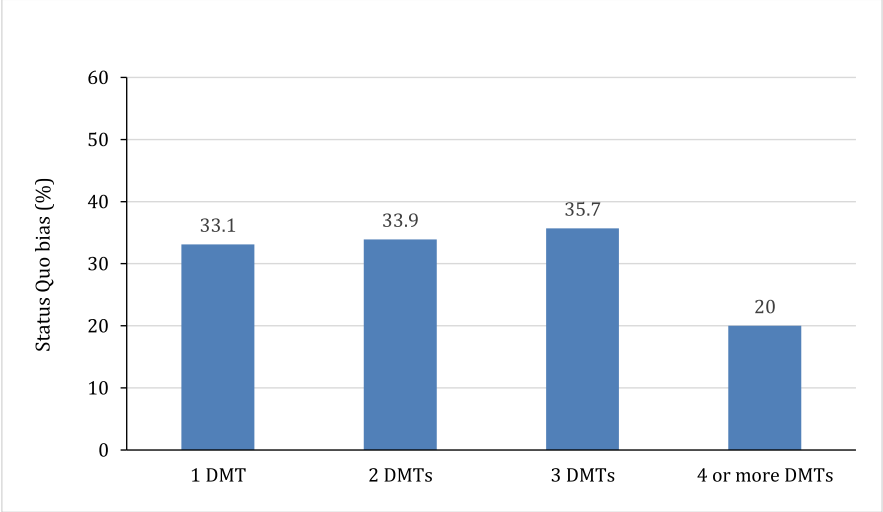


Fig. 2. Status quo bias (SQ) by quartiles of SMSS (Panel A) and DMT exposure (Panel B)
DMT: disease-modifying therapy; SMSS: SymptoMScreen questionnaire.

MS treatments (adjusted OR 1.04; 95% CI 1.01-1.07) (Table 3, Fig. 3, and Appendix). Mixed linear regression models suggest that for every point increase in SMSS, there was a 4% increase in the likelihood of SQ bias (β coefficient 0.04; 95%CI 0.015-0.06; $p < 0.002$) (Appendix). Other outcome measures are summarized in Table 3. The number of previous exposures to DMTs was associated with SQ bias score ($p = 0.032$), but did not reach significance in the multilevel mixed-effects logistic regression (Appendix). SQ bias was more common among simulated-case-scenarios who were already receiving treatment compared to those who were treatment naïve (31.3% vs 12.8%; McNemar test p-value < 0.0001). Our results were also consistent in the sensitivity analysis after adding living status (alone vs. partner/caregiver) or marital status to the models. None of those variables was significant in any of the models (data not shown).

Finally, we attempted to specify which component of the SMSS score was associated with SQ bias. Among the different symptomatic dimensions included in the SMSS, spasticity, bladder control, vision, cognition, depression, and anxiety were associated with SQ bias in the univariate analysis. The multivariate analysis revealed that only vision impairment (β coefficient 0.32; 95%CI 0.05-0.50) and depression (β coefficient 0.29; 95%CI 0.006-0.58) remained associated with SQ bias. The adjusted models with SMSS showed better performance than the models containing depression and vision impairment (c-statistics for SQ: 0.767 vs 0.685; $p = 0.015$; c-statistics for SQ bias score: 0.726 vs 0.643; $p = 0.006$).

3. Discussion

Most neurologists traditionally make therapeutic decisions in MS based on the presence of clinical relapses and MRI findings of disease activity (e.g. gadolinium-enhancing T1 lesions, new or enlarging hyperintense T2 lesions) (Montalban et al., 2018). Patients' perceptions of their functional status and beliefs about their medical condition and how they may influence therapeutic decisions have been inadequately studied (Visser et al., 2020). Our study showed that an inferior therapeutic option was preferred by over 70% of participants with RRMS when treatment escalation was warranted according to best practice recommendations. The presence of SQ bias in at least 50% or more of simulated case-scenarios was observed in over one-third of participants. Patients' individual perception of MS impact was the single

Table 3
Multivariate analysis for the primary and secondary outcome measures

Outcome measures	Mild perception of symptoms (n = 107)	Moderate to severe perception of symptoms (n = 104)	Difference between groups	Multivariate regression analysis (95%CI); p-value
Primary outcome				
Participant-level analysis				
SQ bias score, mean (± SD)	2.63 (1.95)	3.00 (2.03)	(0.37)	0.04 (0.015; 0.06); p = 0.002 †
SQ4 (SQ bias in 4 or more case-scenarios), n (%)	30 (28.0)	44 (42.3)	(14.3)	1.05 (1.02; 10.8); p < 0.001 *
SQ bias (present vs. absent) in at least 1 case scenario, n (%)	76 (71.0)	81 (77.9)	(6.9)	1.04 (1.01; 1.07); p < 0.001 *
Individual responses	n = 1070	n = 1040		
SQ bias, mean (± SD)	26.2 (22.3)	30.0 (28.0)	(3.8)	0.03 (0.003; 0.07); p = 0.03 ‡
SQ4 (SQ bias in 4 or more case-scenarios), n (%)	155/1070 (14.5)	216/1040 (20.8)	(6.3)	1.05 (1.02; 1.08); p < 0.001 ‡

EDSS: Expanded Disability Status Scale; SD: standard deviation; SQ: status quo.
Mild symptoms defined as SMSS (Q1 + Q2), whereas moderate to severe self-perception of symptoms was defined by Q3 + Q4 of SMSS.
All models adjusted for age, EDSS, time since MS diagnosis, number of relapses, number of relapses in the last year, number of DMTs, risk preference, and SMSS as a continuous variable).

* Derived from multivariate logistic regression analysis with SQ4 and SQ bias (present vs. absent) as dependent variable. C-statistics for SQ4: 0.71 and for SQ bias: 0.72

† Derived from linear regression models and expressed in β coefficients (95%CI) with SQ bias score as dependent variable. SQ bias scores were significantly higher among participants with higher SMSS values after adjustment for the pre-specified variables.

‡ Derived from multilevel mixed effects models expressed as OR (95%CI) for binary outcomes (SQ4) and β coefficients (95%CI) for the SQ bias score.

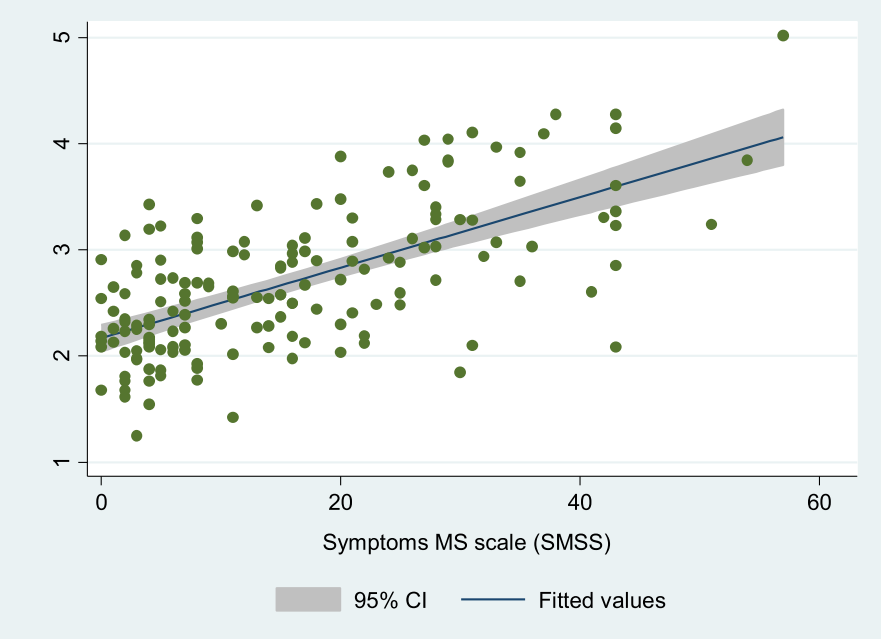


Fig. 3. Observed and predicted probability of Status quo bias in relation to patient's perception of MS severity assessed by SymptoMScreen
SMSS: SymptoMScreen questionnaire.

independent predictor of SQ bias. Our findings are even more surprising when considering the apparently benign characteristics of our study population (median EDSS 2 [IQR 1.0-2.5], with a low average number of relapses in the last year (median 0.4, IQR [0-1]) and a long elapsed time since the last relapse [mean 22.6 (12.9) months].

Given the increasing amount of treatments available, patients play a more important role in shared decisions (either treatment initiation or escalation) with their neurologist (Arroyo et al., 2017). Individual thoughts or negative perceptions towards some agents may not always be openly shared with healthcare professionals, impacting on therapeutic decisions and adherence (Colligan et al., 2017; Wilski et al., 2019). Other studies has reported on the relevance of the development of patients' awareness and self-regulation about their MS trajectory and the role of the treating physician in communicating the prognosis (Colligan et al., 2017).

In this context, there are external and internal factors influencing patients´ therapeutic choices (Saposnik and Montalban, 2018). Among the external factors that have been classically related to treatment decisions, the main ones are age, time from MS diagnosis, disability stage or number of previous treatments used (Saposnik and Montalban, 2018). Internal factors include depression, subjective disability perception or having higher risk-seeking personality (Saposnik and Montalban, 2018). Wilski et al showed that a worse self-perception of physical condition and illness in MS patients was associated with beliefs of negative treatment efficacy (Wilski et al., 2019). Depression also emerged as one of the cardinal symptoms that correlated with poor self-rated health, but not vision impairment (Green et al., 2017). Consistent with other studies, patients are more fearful about the side effects of the medication than impact of the disease itself, and this is enhanced among those with an overly negative

perception of their functional status (Visser et al., 2020; Arroyo et al., 2017). Patients' beliefs may lead to erroneous prognosis forecasting leading to poorer quality of life and increasing SQ bias (Dennison et al., 2018). For example, patients' belief of MS being incurable can dominate attitudes and prevent escalation or attempts to optimize treatment.

Treatment decisions in MS are dynamic and subjectively influenced by patients' experiences of illness and healthcare (Eskyte et al., 2019). Our study is in line with our previous research on therapeutic inertia among treating neurologists suggesting a general knowledge-to-action gap affecting both sides of the physician-patient relationship (Saposnik et al., 2017a). Indeed, this relationship in patients could be affected by cognitive (e.g., pessimistic beliefs about symptom relief and preventing disability progression), emotional (e.g., increased depression/lower mood, fear of side effects) and motivational (e.g., increased apathy/reduced goal directed action) components, with each leading to knowledge-to-action gaps (Eskyte et al., 2019; Wilski et al., 2019; Yalachkov et al., 2019). We may speculate that patients´ negative perception of their own clinical status (and perhaps a sense of helplessness toward the future) is one of the factors that may lead to the SQ bias (Joiner et al., 2001). This feeling of hopelessness is difficult to assess in routine clinical practice, which leads to gaps in managing the patient's expectations and advancing treatment when warranted by best practice recommendations.

Our study has several limitations that deserve mention. First, our study population may not be representative of the entire spectrum of RRMS patients (e.g. EDSS >5) as the great majority of participants had an EDSS lower than 3. Second, we cannot completely rule out the possibility that SQ bias is influenced by other factors that have been included in this study (e.g. type of DMT characteristics or other unmeasured confounders). Third, the lack of information on the treating neurologist (e.g., presence of therapeutic inertia) may have influenced patient´s decisions and SQ bias. In addition, we do not have information about what the treating neurologist would do or recommend in the simulated case-scenarios presented to the study participants, since our aim was to assess only patients with RRMS. Other factors that may attenuate this criticism include results from a recent review showing that contextual factors, patients' preferences and beliefs in everyday life are equally or even more important than clinical measures when making treatment decisions (Eskyte et al., 2019). Fourth, given the small number and differences between simulated case-scenarios, the comparison of other characteristics associated with SQ bias could not be done. Fifth, some variables provided by the treating physician were missing in 20-24% of participants due to a failure with reporting the matching number. However, the baseline characteristics of our study are similar to other survey-based and cohort studies reported in other countries (Fitzgerald et al., 2019). Despite these limitations, our study revealed critical insights into how patients' beliefs and subjective perception of symptom severity influence their willingness to accept treatment escalation, thus limiting the use of more efficacious therapeutic choices when recommended by best practice guidelines. One in three patients with mild MS are not willing to switch to agents that offer more protection in more than 50% of the simulated scenarios presented. Similarly, one in five patients makes suboptimal therapeutic choices despite having a low number of relapses, a low level of disability, and not having symptoms of depression.

4. Conclusion

The landscape of MS treatment is changing rapidly. As different disease-modifying therapies are available, they bring new opportunities to achieve better clinical outcomes. However, our study found that status quo bias affected 7 out of 10 patients with RRMS. This phenomenon appears to be driven by patients' negative self-perception of their clinical status.

Further studies are needed to determine the magnitude of the cognitive, emotional and behavioral components leading to status quo bias among RRMS patients.

CRediT authorship contribution statement

Gustavo Saposnik: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Javier Sotoca:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Ángel P. Sempere:** Methodology, Writing - review & editing. **Antonio Candeliere-Merlicco:** Data curation, Methodology. **Paola Díaz-Abós:** Methodology, Writing - review & editing. **Philippe N. Tobler:** Methodology, Writing - review & editing. **María Terzaghi:** Methodology, Writing - review & editing. **Jorge Maurino:** Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102354.

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