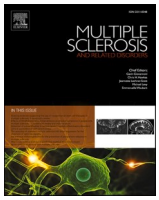
Multiple Sclerosis and Related Disorders 60 (2022) 103706

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Real-world disease-modifying therapy usage in persons with relapsing-remitting multiple sclerosis: Cross-sectional data from the Swiss Multiple Sclerosis Registry

Jonas Bossart [a,b,1], Christian P. Kamm [c,d,1], Marco Kaufmann [a], Mina Stanikić [a,e], Milo A. Puhan [a], Jürg Kesselring [f], Chiara Zecca [g,h], Claudio Gobbi [g,h], Irene Rapold [a], Roland Kurmann [a], Sabin Ammann [a], Viktor von Wyl [a,e,*], for the Swiss Multiple Sclerosis Registry (SMSR)

[a] *Epidemiology, Biostatistics and Prevention Institute, University of Zurich (UZH), Hirschengraben 84, Zurich 8001, Switzerland*
[b] *Department of Materials Meet Life, Particles-Biology Interactions, Swiss Federal Laboratories for Materials Science and Technology (Empa), St. Gallen, Switzerland*
[c] *Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland*
[d] *Neurocentre, Luzerner Kantonsspital, Lucerne, Switzerland*
[e] *Institute for Implementation Science in Health Care, University of Zurich (UZH), Zurich, Switzerland*
[f] *Department of Neurology and Neurorehabilitation, Rehabilitation Center Valens, Valens, Switzerland*
[g] *Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland*
[h] *Department of Neurology, Multiple Sclerosis Center, Neurocenter of Southern Switzerland, EOC, Lugano, Switzerland*

ARTICLE INFO

Keywords:
Relapsing-remitting multiple sclerosis
Disease-modifying therapy
Cross-sectional analysis
Real-world
Switzerland

ABSTRACT

Introduction: Several disease-modifying therapies (DMTs), covering a broad spectrum of mechanisms of action, have been approved by regulatory agencies for the treatment of relapsing-remitting multiple sclerosis (RRMS). However, only little is known about the current real-world treatment situation in Switzerland. Based on data from a diverse population of 668 persons with RRMS from the Swiss Multiple Sclerosis Registry (SMSR), the present study aims to fill this gap with a descriptive, cross-sectional approach.
Methods: Data originated from the SMSR baseline questionnaire and follow-up surveys. Data on current health status and life situation in the last 6 months were extracted from the survey distributed throughout 2020 and 2021, while data on disease-modifying therapy (DMT) histories were included from preceding surveys. Initially, data was stratified into three DMT groups according to the current DMT status (*NO* (No DMT), *CONTINUED* (DMT started more than 6 months ago), and *NEW* (DMT started less than 6 months ago)). In a subsequent analysis, the sample was stratified into groups corresponding to the five most frequently prescribed DMTs. Self-reported outcomes including therapy discontinuation or interruption, relapses and side-effects in the last 6 months were analyzed per group. Life and health situation parameters were also determined and analyzed.
Results: The study population consisted of 445 (66.6%) individuals belonging to the *CONTINUED*, 84 (12.6%) to the *NEW*, and 139 (20.8%) to the *NO* group. Within the *NO* group, 24 (17.3%) reported relapses. Furthermore, self-reported relapses (28 (33.3%)), side-effects (39 (46.4%)), and treatment discontinuations or interruptions (30 (35.7%)) occurred more frequently in the *NEW* compared to the *CONTINUED* group (37 (8.3%), 125 (28.1%), 8 (1.8%), respectively). The three groups also differed with respect to age, time since diagnosis, number of symptoms, DMT history, and health-related quality of life. The five most frequently prescribed DMTs included fingolimod (33.4%), dimethyl fumarate (25.0%), ocrelizumab (23.6%), natalizumab (10.6%) and teriflunomide (7.5%). The frequency of self-reported relapses ranged from 9.7% to 13.6%. Notable differences were found in the number of self-reported side-effects, ranging from 9.1% with natalizumab to 56.7% with dimethyl fumarate.
Discussion: This cross-sectional analysis suggested that the majority of individuals with RRMS in Switzerland continuously receive tolerable DMT. However, groups not receiving DMT or struggling with side-effects or continued disease worsening while on DMT still persist. It is conceivable that the number of self-reported

* Corresponding author at: Epidemiology, Biostatistics and Prevention Institute, University of Zurich (UZH), Hirschengraben 84, Zurich 8001, Switzerland
E-mail address: viktor.vonwyl@uzh.ch (V. von Wyl).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.msard.2022.103706
Received 1 December 2021; Received in revised form 10 February 2022; Accepted 19 February 2022
Available online 21 February 2022

symptoms indicates the need for more detailed clarification of the DMT characteristics and expectations of treatment outcomes. Injectable DMTs no longer play a major role in the treatment of RRMS in Switzerland and a trend toward an early use of potent drugs is emerging.

1. Introduction

Although modern disease-modifying therapies (DMTs) can reduce relapse rates and slow down the disease worsening in persons with relapsing-remitting multiple sclerosis (RRMS), they require a careful, joint risk-benefit assessment by both neurologists and persons with MS (PwMS) (Coret et al., 2018; Spanu et al., 2020; Tanasescu et al., 2014; Wingerchuk and Carter, 2014). Thereby, the expected benefit of DMTs must be weighed against, among others, side-effects known from clinical trials, but also potential adverse effects reported in extension studies and case reports (Jalkh et al., 2021).

However, the decision-making process is hampered because of limited real-world evidence and challenges, which may differ markedly from pivotal trials of novel drugs performed in selected participants and highly specialized settings. For example, treating neurologists need to consider not only tolerability of potential side-effects, but also comorbidities, advanced age, and other concomitant treatments. Therefore, real-world analyses including participants independently of care setting or treatment status, are of great importance to gather insights into the real-world effectiveness of DMTs. Such studies have been conducted, but mostly in specialized populations or with a limited age range (Braune et al., 2021; Spelman et al., 2021; Turčáni et al., 2020). Furthermore, there is increasing awareness by regulatory agencies for the need to include patient-reported outcomes along with clinical outcomes in decision making. To the best of our knowledge, currently there is no comprehensive study describing the current real-world situation with respect to disease-modifying therapy (DMT) use in Switzerland.

By leveraging data from a nationwide MS registry with broad enrollment criteria, comprehensive self-reported treatment and disease history, and continuous collection of symptom and disease status measures, we sought to characterize the population of persons with RRMS in Switzerland with respect to the use of and self-reported outcomes of DMT. In a cross-sectional analysis of a standardized follow-up survey conducted in 2020 and 2021, we aimed to explore.

(1) How many PwMS were on new (DMT started less than 6 months ago), continued (DMT started more than 6 months ago) or no DMT?
(2) How did persons differ across the three DMT groups with respect to socio-demographic, MS- and treatment-related characteristics?
(3) Which undesirable treatment effects were reported for the five most frequently used DMTs in the study population?

Combined, these analyses contribute to better understanding of the real-world treatment situation, as well as potential reasons for treatment changes or non-uptake of DMT among persons with RRMS in Switzerland.

2. Methods

2.1. Origin of data

The analysis was conducted on data of the Swiss Multiple Sclerosis Registry (SMSR). The SMSR, operated by the University of Zurich, was founded in 2016, following the approval by the Ethics Committee of the Canton of Zurich (PB-2016–00894; BASEC-NR 2019–01027). The innovative citizen science approach of the SMSR combines the advantages of traditional and modern research methods (Steinemann et al., 2018). Moreover, the approach is prospective and particularly benefits from a diverse study population independent of the type of healthcare institution where MS is being managed (Puhan et al., 2018). The SMSR further benefits from the wide network of the Swiss MS Society and the existence of various media outlets, such as website, member magazines and social media (Steinemann et al., 2018). This allows a nationwide dissemination of information about the SMSR to PwMS and involved medical personnel, which facilitates the self-recruitment and peer referral recruitment process. Regular SMSR semi-annual questionnaires can be answered digitally or on paper, and phone interviews are offered in some cases. To date, the SMSR has collected data of more than 2′500 adult PwMS. To ensure data integrity and fulfill ethical considerations, participants were required to provide written informed consent and confirmation of the MS diagnosis from their treating physician (Puhan et al., 2018).

Data used in the present study originated from the SMSR baseline and follow-up surveys. Baseline survey provided socio-demographic data, while information on current DMT usage, health status and life situation reflecting the last 6 months stemmed from a follow-up survey distributed between February 2020 and April 2021 (Puhan et al., 2018; Steinemann et al., 2018). Additionally, history of DMT usage was constructed from preceding surveys.

2.2. Analysis

Selection of the participants for the final study sample is illustrated in **Fig. 1**. For study aims 1 and 2, the population was stratified into three DMT groups (**Fig. 2**): *NO* (No DMT), *CONTINUED* (DMT started more than 6 months ago, which includes DMT continued at least until the date of survey response as well as DMT stopped or interrupted within the 6-month timeframe), and *NEW* (DMT started less than 6 months ago). To address study aim 3, we selected the five most frequently used DMTs in the years 2020 and 2021 (i.e. within the last follow-up survey).

Outcomes of interest included the occurrence of relapses (categorical), discontinuation or interruption of therapy (categorical), and the occurrence of side-effects (categorical), all within the past 6 months.

The following additional factors were compared across treatment groups (aims 1 and 2), as well as across the five most frequently used DMTs (aim 3): Gender (categorical), language region (categorical), age (continuous and categorical), time since MS diagnosis (continuous and categorical), MS diagnosis in the last 3 years (categorical), symptoms (categorical) and number of symptoms (continuous and categorical), side-effects (categorical), DMT route of administration (categorical), total number of DMTs used including current treatment (continuous and categorical), how many (continuous), non-pharmacological and alternative medical therapies (categorical), Self-Reported Disability Status Scale (SRDSS, a validated self-reported approximation of the EDSS, categorical) (Kaufmann et al., 2020), presence of comorbidities (categorical), total Modified Fatigue Impact Scale, a multidimensional scale, which includes physical, psychological, and cognitive aspects of fatigue (MFIStotal, continuous) (The Council, 1998; Fischer et al., 1999; Learmonth et al., 2013), clinical relevance of MFIStotal (categorical, cutoff value 38) (Flachenecker et al., 2002), EuroQol-5 dimension Index, being an index describing health-related quality of life, incorporating 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (EQ-5D-Index, continuous, French scale, rescaled to 0–100) (Brooks, 1996; EuroQol, 1990; Rabin and De Charro, 2001) and Visual Analogue Scale, a self-reported value between 0 and 100 intended to describe the current health status (VAS, continuous and categorical).

Both the outcomes of interest and the additional factors were self-reported. For each question, persons with RRMS were asked to select one or multiple possible answers from a predefined selection, with a free

text field available for additional comments as well. Furthermore, there were questions with unrestricted answer options, for example for year numbers.

If participants had less or equal to five missing values across previously mentioned additional parameters, their data was included in the analysis dataset. Data was analyzed descriptively. Grouped number of mentions and percentages were reported for categorical variables, mean and standard deviation for continuous variables. Due to the large number of comparisons and the descriptive nature of our study, we deliberately decided not to calculate *p*-values.

Multiple imputation by chained equations (MICE) was implemented (Rubin, 1996), and the imputed dataset was used for sensitivity analyses. To assess the transportability of our findings, socio-demographic factors of the included sample were compared against the characteristics of the entire SMSR RRMS population. The entire data processing and analysis was carried out in Python version 3.8.5 (Van Rossum and Drake, 2009). The Python library scikit-learn version 0.24.2 was used for imputation (Pedregosa et al., 2011).

3. Results

In total, 1075 PwMS completed the last follow-up survey, including 685 persons with RRMS: Data of 668 persons with RRMS were included in the analysis (Fig. 1).

3.1. Classification of persons with RRMS by DMT status (aim 1)

As shown in Fig. 2, 445 (66.6%) participants belonged to the *CONTINUED* group, of whom 208 (46.7%) reported to receive their first DMT (Table 1).

Furthermore, 139 PwMS (20.8%) reported to not have been treated in the last 6 months and therefore belong to the *NO* group. Within this group, 53 (38.1%) reported never having received a DMT, 49 (35.3%) who had one therapy in the past and 37 (26.6%) PwMS who had several therapies.

Lastly, 84 (12.6%) participants were assigned to the *NEW* group, whereby 54 (64.3%) participants were prescribed the very first treatment, while the rest of the group was prescribed a new DMT after having

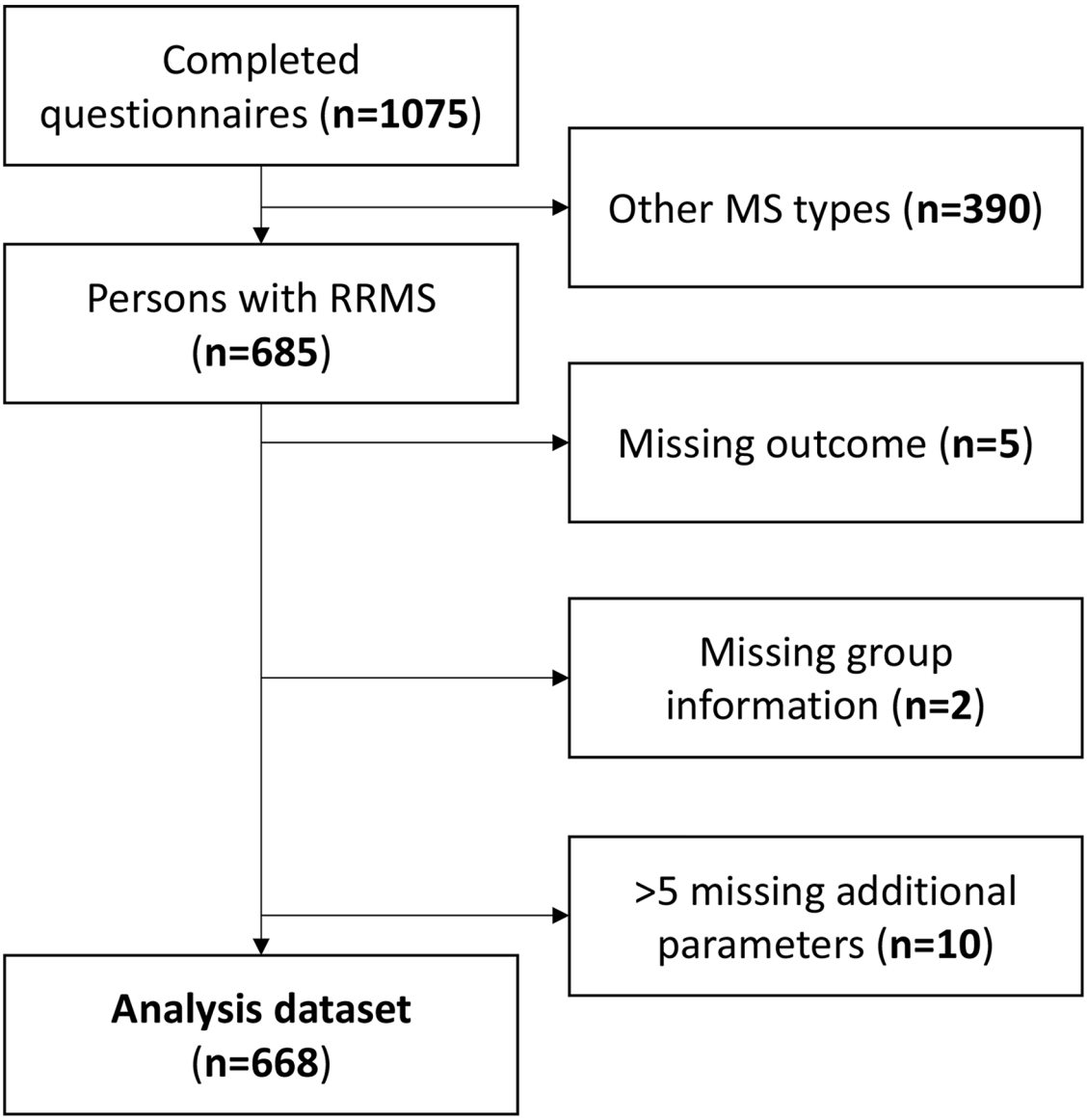


Fig. 1. Flowchart of data processing with the respective number of received questionnaires. Based on 1′075 completed questionnaires in this assessment wave, submitted between February 2020 and April 2021, persons with RRMS with known information regarding the three outcomes and grouping (use of DMT) were selected. After matching with baseline health and socio-demographic parameters, entries with not more than five missing values were included.

received a different DMT in the past.

3.2. Socio-demographic, disease- and treatment-related characteristics per DMT-based group (aim 2)

Relapses in the last 6 months prior to the survey were most frequently reported in persons belonging to the *NEW* group (28, 33.3%), followed by the *NO* group (24, 17.3%) and least frequently in persons belonging to the *CONTINUED* group (37, 8.3%).

In the 6-month period before the survey, 125 (28.1%) persons in the *CONTINUED* and 39 (46.4%) in the *NEW* group reported the occurrence of side-effects (Table 1).

As shown in Fig. 2, in the *CONTINUED* group 8 persons reported treatment interruption or discontinuation, out of which 2 (0.4%) were due to side-effects [leukopenia and an unknown side-effect], 2 (0.4%) due to disease worsening [each once with and without relapse] and 4 (0.9%) persons reported interruptions/discontinuations due to other or multiple reasons [a current and a planned pregnancy, a person who would like to avoid medication in the future and another unknown reason]. Among these 8 mentioned interruptions or discontinuations 3 PwMS (37.5%) were receiving their first DMT. Of 30 PwMS reporting DMT discontinuation or interruption in the *NEW* group, 12 (14.3%) persons (6 received their first and 6 received subsequent DMT) cited side-effects as reasons for discontinuation/interruption, among which allergies, skin problems, leukopenia and avoidance of progressive multifocal leukoencephalopathy were frequently observed. 8 (9.5%) persons stated disease worsening [relapse in 4 out of 8] was the reason for discontinuation or interruption, and 10 (11.9%) mentioned multiple or other reasons [three combinations of side-effects and worsening, two (planned) pregnancies, and one mention each of inconvenient handling, change in medication, intentional interruption, fear of SARS-CoV-2 infection, and one other unknown reason].

Characteristics of the three DMT-based groups are shown in Table 1. Age, time since diagnosis and clinical relevance of the total MFIS differed across all groups. Other characteristics only exhibited noticeable differences between persons receiving *CONTINUED* and *NEW* therapies, but less so between the *NO* and *CONTINUED* groups. Specifically, in the *NEW* group, the proportion of persons who were diagnosed with MS within the last three years was higher (47, 56.0%) when compared with the *CONTINUED* (59, 13.3%) and *NO* (16, 11.5%) groups. Similarly, the average number of symptoms in the last 6 months and the proportion of persons with SRDSS > 3.5 were also higher in the *NEW* group when compared to both *CONTINUED* and *NO* groups.

Regarding non-pharmacological and alternative medical treatments, several such treatments were reported in each group. Vitamin (vitamin B excluded) and mineral supplements (170, 25.4%), physiotherapy (120, 18.0%) and vitamin B supplements (99, 14.8%) were mentioned most frequently. Between the three groups, there were no major differences regarding non-drug and alternative medical treatments. However, alternative treatments such as osteopathy, naturopathy and homeopathy were predominantly observed in the *NO* group.

With respect to self-reported outcomes, average health-related quality of life as measured by the EQ-5D-Index was lower in the *NEW* group (78.8, SD 17.3) when compared with the *CONTINUED* (84.3, SD 15.3) and *NO* groups (82.9, SD 14.0). However, the variation was high. Furthermore, the *NEW* group had the highest proportion of persons with an MFIS-score above the critical threshold of 38 (31, 36.9%), followed by the *NO* group (45, 32.4%) and the *CONTINUED* group (114, 25.6%).

3.3. Comparison of five most frequently reported DMTs (aim 3)

The five most frequently reported DMTs were fingolimod (139, 33.4%), followed by dimethyl fumarate (104, 25.0%), ocrelizumab (98, 23.6%), natalizumab (44, 10.6%) and teriflunomide (31, 7.5%). Of those five DMTs, ocrelizumab was most frequently reported by the participants in the group *NEW* (23, 23.5%), while fingolimod was on the other side of spectrum (7, 5.0%). More than 50% of participants in the fingolimod (72, 51.8%), dimethyl fumarate (57, 54.8%), and

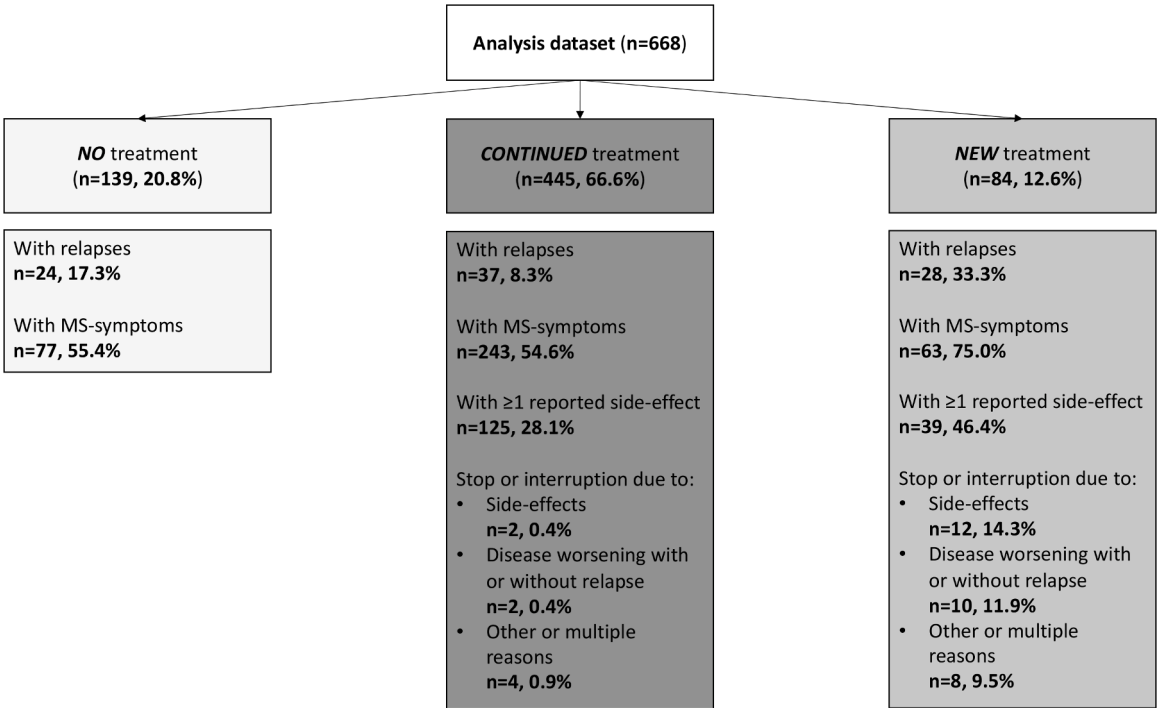


Fig. 2. Chart showing the respective number and percentages of three groups, depending on DMT start (if applicable). The groups include *NO* (no DMT), *CONTINUED* (DMT started more than 6 months ago, which includes DMT continued at least until the date of survey response as well as DMT stopped or interrupted within the 6-month timeframe) and *NEW* (DMT started less than 6 months ago), using the 6 months prior to survey completion as a reference. It also shows how often participants reported relapses and MS symptoms (at least one symptom reported) (all), as well as how often side-effects and interruptions or discontinuations occurred (two therapy groups).

Table 1
Socio-demographic and disease characteristics of persons with RRMS ($n = 668$), grouped by DMT (*NO, CONTINUED* and *NEW* treatment).

	NO treatment	***CONTINUED*** treatment	***NEW*** treatment	**Overall**
Variable				
N	139 (20.8%)	445 (66.6%)	84 (12.6%)	668
Sex				
Male	32 (23.0%)	98 (22.0%)	18 (21.4%)	148 (22.2%)
Female	107 (77.0%)	347 (78.0%)	66 (78.6%)	520 (77.8%)
Language region				
German	108 (77.7%)	374 (84.0%)	64 (76.2%)	546 (81.7%)
French	24 (17.3%)	58 (13.0%)	15 (17.9%)	97 (14.5%)
Italian	7 (5.0%)	13 (2.9%)	5 (6.0%)	25 (3.7%)
Age (mean, SD)	49.3 (11.2)	46.4 (10.8)	43.2 (11.6)	46.6 (11.1)
Age				
<50 years	67 (48.2%)	270 (60.7%)	60 (71.4%)	397 (59.4%)
≥50 years	72 (51.8%)	175 (39.3%)	24 (28.6%)	271 (40.6%)
Relapse in the last 6 months				
No	115 (82.7%)	408 (91.7%)	56 (66.7%)	579 (86.7%)
Yes	24 (17.3%)	37 (8.3%)	28 (33.3%)	89 (13.3%)
Therapy discontinuation or interruption in the last 6 months				
No	–	437 (98.2%)	54 (64.3%)	491 (92.8%)
Yes	–	8 (1.8%)	30 (35.7%)	38 (7.2%)
Side-effect in the last 6 months				
No	–	320 (71.9%)	45 (53.6%)	365 (69.0%)
Yes	–	125 (28.1%)	39 (46.4%)	164 (31.0%)
Tiredness, Fatigue	–	38 (8.5%)	13 (15.5%)	51 (9.6%)
Hot flushes	–	39 (8.8%)	10 (11.9%)	49 (9.3%)
Others	–	33 (7.4%)	16 (19.1%)	49 (9.3%)
Headache	–	36 (8.1%)	7 (8.3%)	43 (8.1%)
Intestinal dysfunction, Digestive problems	–	25 (5.6%)	8 (9.5%)	33 (6.2%)
Skin problems	–	26 (5.8%)	5 (6.9%)	31 (5.9%)
Flu symptoms	–	21 (4.7%)	8 (9.5%)	29 (5.5%)
Pain	–	21 (4.7%)	6 (7.1%)	27 (5.1%)
Dizziness	–	19 (4.3%)	3 (3.6%)	22 (4.2%)
Sleeping problems, Insomnia	–	15 (3.4%)	6 (7.1%)	21 (4.0%)
Hair loss	–	11 (2.5%)	3 (2.6%)	14 (2.6%)
Allergic reaction	–	8 (1.8%)	5 (6.0%)	13 (2.5%)
Depression	–	7 (1.6%)	3 (3.6%)	10 (1.9%)
Opportunistic infection	–	9 (2.0%)	0 (0.0%)	9 (1.7%)
Manic or psychotic symptoms	–	1 (0.2%)	1 (1.2%)	2 (0.4%)
Measures to prevent PML	–	0 (0.0%)	2 (2.4%)	2 (0.4%)
Euphoria	–	1 (0.2%)	0 (0.0%)	1 (0.2%)
Time since diagnosis in years (mean, SD)	11.7 (8.6)	10.8 (7.4)	7.6 (6.6)	10.6 (7.6)
Time since diagnosis				
1–3 years	16 (11.5%)	59 (13.3%)	35 (41.7%)	110 (16.5%)
4–10 years	59 (42.5%)	191 (42.9%)	21 (25.0%)	271 (40.6%)
11–20 years	41 (29.5%)	140 (31.5%)	21 (25.0%)	202 (30.2%)
21–30 years	14 (10.1%)	40 (9.0%)	5 (6.0%)	59 (8.8%)
>30 years	6 (4.3%)	8 (1.8%)	0 (0.0%)	14 (2.1%)
Unknown	3 (2.2%)	7 (1.6%)	2 (2.4%)	12 (1.8%)
Recently diagnosed, ≤3 years				
No	120 (86.3%)	379 (85.2%)	35 (41.7%)	546 (81.7%)
Yes	16 (11.5%)	59 (13.3%)	47 (56.0%)	110 (16.5%)
Unknown	3 (2.2%)	7 (1.6%)	2 (2.4%)	12 (1.8%)
Number of symptoms in the last 6 months (mean, SD)	3.4 (4.3)	3.5 (4.3)	4.8 (4.5)	3.7 (4.3)
Number of symptoms in the last 6 months				
0	62 (44.6%)	202 (45.4%)	21 (25.0%)	285 (42.7%)
1	9 (6.5%)	15 (3.4%)	5 (6.0%)	29 (4.3%)
2–3	17 (12.2%)	55 (12.4%)	16 (19.1%)	88 (13.2%)
4–5	10 (7.2%)	43 (9.7%)	9 (10.7%)	62 (9.3%)
6–7	12 (8.6%)	46 (10.3%)	9 (10.7%)	67 (10.0%)
8–9	14 (10.1%)	30 (6.7%)	9 (10.7%)	53 (7.9%)
>9	15 (10.8%)	54 (12.1%)	15 (17.9%)	84 (12.6%)
Symptoms in the last 6 months				
Tiredness, Fatigue	51 (36.7%)	176 (39.6%)	46 (54.8%)	273 (40.9%)
Paresthesia	53 (38.1%)	166 (37.3%)	50 (59.5%)	269 (40.3%)
Pain	38 (27.3%)	108 (24.3%)	28 (33.3%)	174 (26.0%)
Concentration problems	33 (23.7%)	111 (24.9%)	26 (31.0%)	170 (25.4%)
Weakness	32 (23.0%)	103 (23.2%)	28 (33.3%)	163 (24.4%)
Balance disorders	29 (20.9%)	105 (23.6%)	26 (31.0%)	160 (24.0%)
Gait abnormalities	29 (20.9%)	92 (20.7%)	18 (21.4%)	139 (20.8%)
Bladder disorders	18 (13.0%)	84 (18.9%)	15 (17.9%)	117 (17.5%)
Spasms	23 (16.6%)	71 (16.0%)	22 (26.2%)	116 (17.3%)
Dizziness	19 (13.7%)	74 (16.6%)	20 (23.8%)	113 (16.9%)
Memory disorders	17 (12.2%)	80 (18.0%)	16 (19.0%)	113 (16.9%)
Intestinal dysfunction	16 (11.5%)	68 (15.3%)	14 (16.7%)	98 (14.7%)
Impaired vision	26 (18.7%)	50 (11.2%)	15 (17.9%)	91 (13.6%)
Depression		41 (9.2%)		

(*continued on next page*)

Table 1 (*continued*)

	NO treatment	***CONTINUED*** treatment	***NEW*** treatment	**Overall**
	18 (13.0%)		11 (13.1%)	70 (10.5%)
Sexual disorders	8 (5.8%)	50 (11.2%)	11 (13.1%)	69 (10.3%)
Affective lability	11 (7.9%)	32 (7.2%)	12 (14.3%)	55 (8.2%)
Tremor	12 (8.6%)	33 (7.4%)	8 (9.5%)	53 (7.9%)
Language disorders	11 (7.9%)	31 (7.0%)	9 (10.7%)	51 (7.6%)
Paralysis symptoms	6 (4.3%)	29 (6.5%)	10 (11.9%)	45 (6.7%)
Twitching, Tics	12 (8.6%)	21 (4.7%)	8 (9.5%)	41 (6.1%)
Dysphagia	6 (4.3%)	11 (2.4%)	7 (8.3%)	24 (3.6%)
Problems with spatial orientation	3 (2.2%)	16 (3.6%)	3 (3.6%)	22 (3.3%)
Others	4 (2.9%)	4 (0.9%)	2 (2.4%)	10 (1.5%)
Epileptic seizure	0 (0.0%)	2 (0.5%)	0 (0.0%)	2 (0.3%)
DMT route of administration				
None	139 (100%)	0 (0.0%)	0 (0.0%)	139 (20.8%)
Injection	0 (0.0%)	77 (17.3%)	7 (8.3%)	84 (12.6%)
Infusion	0 (0.0%)	117 (26.3%)	29 (34.5%)	146 (21.9%)
Oral	0 (0.0%)	251 (56.4%)	27 (32.1%)	278 (41.6%)
Unknown	0 (0.0%)	0 (0.0%)	21 (25.0%)	21 (3.1%)
Number of different DMTs used, including current (mean, SD)	1.2 (1.7)	1.9 (1.1)	1.6 (0.9)	1.7 (1.3)
Number of different DMTs used, including current				
0	53 (38.1%)	0 (0.0%)	0 (0.0%)	53 (7.9%)
1	49 (35.3%)	208 (46.7%)	54 (64.3%)	311 (46.6%)
>1	37 (26.6%)	237 (53.3%)	30 (35.7%)	304 (45.5%)
Number of non-pharmacological and alternative medical treatments in the last 6 months (mean, SD)	1.5 (2.0)	1.2 (1.7)	1.3 (1.6)	1.3 (1.7)
Non-pharmacological and alternative medical treatments in the last 6 months				
Other vitamin and mineral supplements	45 (32.4%)	105 (23.6%)	20 (23.8%)	170 (25.4%)
Physiotherapy	17 (12.2%)	86 (19.3%)	17 (20.4%)	120 (18.0%)
Vitamin B supplements	29 (20.9%)	61 (13.7%)	9 (10.7%)	99 (14.8%)
Others	19 (13.7%)	56 (12.6%)	17 (20.4%)	92 (13.8%)
Relaxation therapies	14 (10.1%)	41 (9.2%)	10 (11.9%)	65 (9.7%)
Naturopathy	20 (14.4%)	31 (7.0%)	10 (11.9%)	61 (9.1%)
Osteopathy	16 (11.5%)	26 (5.8%)	2 (2.4%)	44 (6.6%)
Homeopathy	16 (11.5%)	24 (5.4%)	4 (4.8%)	44 (6.6%)
Psychotherapy	8 (5.8%)	24 (5.4%)	7 (8.3%)	39 (5.8%)
Acupuncture	9 (6.5%)	22 (4.9%)	3 (3.6%)	34 (5.1%)
Occupational therapy	5 (3.6%)	9 (2.0%)	2 (2.4%)	16 (2.4%)
Cranberry juice	8 (5.8%)	8 (1.8%)	0 (0.0%)	16 (2.4%)
Nutritional therapy	1 (0.7%)	8 (1.8%)	5 (6.0%)	14 (2.1%)
Hippotherapy	4 (2.9%)	9 (2.0%)	1 (1.2%)	14 (2.1%)
Aromatherapy	3 (2.2%)	4 (0.9%)	1 (1.2%)	8 (1.2%)
Trigger point therapy	0 (0.0%)	5 (1.1%)	2 (2.4%)	7 (1.0%)
Neuropsychological therapy	1 (0.7%)	3 (0.7%)	1 (1.2%)	5 (0.7%)
Speech and language therapy	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.3%)
SRDSS				
0–3.5	128 (92.1%)	415 (93.3%)	70 (83.3%)	613 (91.8%)
4–6.5	7 (5.0%)	25 (5.6%)	9 (10.7%)	41 (6.1%)
7–9.5	2 (1.4%)	3 (0.7%)	4 (4.8%)	9 (1.4%)
Unknown	2 (1.4%)	2 (0.5%)	1 (1.2%)	5 (0.8%)
Comorbidity				
No	107 (77.0%)	368 (82.7%)	61 (72.6%)	536 (80.2%)
Yes	30 (21.6%)	75 (16.9%)	21 (25.0%)	126 (18.9%)
Unknown	2 (1.4%)	2 (0.5%)	2 (2.4%)	6 (0.9%)
MFIStotal (mean, SD)	27.9 (19.4)	25.3 (18.9)	32.7 (19.3)	26.8 (19.2)
MFIS clinically relevant, ≥38				
No	86 (61.9%)	312 (70.1%)	49 (58.3%)	447 (66.9%)
Yes	45 (32.4%)	114 (25.6%)	31 (36.9%)	190 (28.4%)
Unknown	8 (5.8%)	19 (4.3%)	4 (4.8%)	31 (4.6%)
EQ-5D-Index, scaled to 0–100 (mean, SD)	82.9 (15.9)	84.3 (14.0)	78.8 (17.3)	83.3 (14.9)
VAS (mean, SD)	79.0 (18.9)	80.9 (16.9)	75.0 (19.3)	79.8 (17.7)
VAS				
0–25	3 (2.2%)	5 (1.1%)	3 (3.6%)	11 (1.7%)
26–50	12 (8.6%)	30 (6.7%)	7 (8.3%)	49 (7.3%)
51–75	30 (21.6%)	90 (20.2%)	24 (28.6%)	144 (21.6%)
76–100	91 (65.5%)	310 (69.7%)	47 (56.0%)	448 (67.1%)
Unknown	3 (2.2%)	10 (2.3%)	3 (3.6%)	16 (2.4%)

teriflunomide (16, 51.6%) groups received their respective treatment as the first DMT ever. Corresponding percentages for ocrelizumab (31, 31.6%) and natalizumab (10, 22.7%) were markedly lower. Therapy interruptions or discontinuations were reported most often in the ocrelizumab group (10, 10.2%) and least in the fingolimod group (1, 0.7%).

The overall proportion of self-reported side-effects varied markedly across the five DMT groups, ranging from 9.1% (4) in the natalizumab group to 56.7% (59) in the dimethyl fumarate group. Types of self-reported side-effects also differed by DMT groups. In each group, the three most frequent side-effects were: Headaches (10, 7.2%), tiredness (7, 5.0%), and skin problems (7, 5.0%) in fingolimod; hot flushes (35, 33.7%), other (21, 20.2%), and digestive problems (16, 15.4%) in dimethyl fumarate; tiredness (12, 12.2%), headache (8, 8.2%), and other (8, 8.2%) in ocrelizumab; tiredness (2, 4.5%), and other (2, 4.5%)

in natalizumab; and skin problems (5, 16.1%), tiredness (4, 12.9%), and digestive problems (4, 12.9%) in teriflunomide (Table 2).

The sensitivity analyses based on imputed datasets are shown in **Supplementary Table 1** and **Supplementary Table 2** and did not materially alter results. A comparison of the included study population with the entire RRMS population enrolled in the SMSR yielded no substantiative differences with respect to age, gender, or disease duration, except for the proportion of persons with a history of DMT use, which was higher in the study population sample, as shown in **Supplementary Table 3**.

4. Discussion

In this cross-sectional analysis of the SMSR with a broad and treatment-setting independent population, a total of 668 persons with RRMS were analyzed. Two out of three PwMS were on a continued DMT, while one out of eight started DMT within the last 6 months. Finally, 1 in 5 persons with RRMS was not receiving DMT. Those who newly started DMT were younger, were more recently diagnosed with MS and had more active disease (with respect to symptom burden) in comparison to the other two groups. While oral and infusion therapies were preferred, no DMT ensured for a burden-free life, neither from MS-symptoms nor treatment side-effects, such as hot flushes or intestinal side-effects.

PwMS in the *NEW* group also reported overall more MS-associated symptoms in the last 6 months prior the survey than the *CONTINUED* or *NO* groups, with paresthesia, fatigue, pain, and concentration problems predominantly mentioned. While a more active disease can be expected among the newly diagnosed and younger PwMS, a larger proportion of PwMS with SRDSS above 3.5 in this group is unexpected, as PwMS with longer disease courses tend to have a higher accumulation of disability (Zeydan and Kantarci, 2020). However, this could reflect symptoms associated with recent diseases activity, as self-reported relapses were more common in the *NEW* group.

In addition to MS-related symptoms, many persons receiving DMT reported side-effects, often not clearly distinguishable from MS symptoms. The *NEW* group reported substantially more side-effects than the *CONTINUED* group which is not surprising as a large portion of side-effects tends to occur early after treatment initiation (Khatri, 2016; Zadeh et al., 2019). The strikingly frequent mention of tiredness and fatigue in connection with unwanted treatment may warrant further investigation, as well as clarifications in neurological consultation. Such symptoms may also be MS-related, and their frequent reports in context of unwanted treatment effects can be suggestive for uncertainty with respect to possible benefits of DMT, which are primarily to reduce the relapse rate and progression and less to reduce the burden of MS symptoms. Neurologists play an important role in clear communication and in supporting expectation management.

Side-effects could be seen as the main reason for a high rate of treatment discontinuation within the first 6 months of therapy. Our findings suggest that once a DMT has been in use for longer than 6 months, treatment discontinuations are quite rare. In the group of PwMS who switched their DMT and were still using DMT (>1 different DMTs used, including current), ocrelizumab and fingolimod were most often reported as the momentary drugs of choice. This shows a clear tendency to use highly potent drugs early in the treatment of MS, as well as favorable profiles of both fingolimod and ocrelizumab with regards to usage of these drugs in JCV-positive patients (Brancati et al., 2021; Farley et al., 2019; Rempe et al., 2020).

Three out of five most frequently administered are oral therapies (fingolimod, dimethyl fumarate and teriflunomide) and two out of five are infusion treatments (ocrelizumab and natalizumab), suggesting that injectables (interferons, glatiramer acetate) no longer have a leading role in Switzerland. Almost all (95%) PwMS treated with fingolimod belonged to the *CONTINUED* group, whereas this was least frequently the case with ocrelizumab treated PwMS (76.5%). On the other hand, ocrelizumab was the most often used treatment in the *NEW* group (23.5%). This is in line with the expectations, as fingolimod was initially approved in 2011 as the first oral first-line treatment in Switzerland, while ocrelizumab was approved in 2017 (Swissmedic, 2021;). Supposedly, PwMS with stable disease and no relevant side-effects under fingolimod continued treatment whilst others were already switched to alternative therapies explaining the high number of PwMS in the *CONTINUED* group. In addition, these findings again suggest an uptake of an aggressive approach in early MS treatment with potent drugs. This is further underlined by the frequent usage of natalizumab, being the second most often reported drug in the *NEW* group (13.6%). Natalizumab was however used less often as first line therapy, possibly explicable by the main indication as an escalation therapy in active RRMS (Swissmedic, 2021). Accordingly, natalizumab was rarely administered to the recently diagnosed PwMS, with teriflunomide being the most frequently reported drug. Both natalizumab and fingolimod were well tolerated, while PwMS using dimethyl fumarate and teriflunomide reported the highest number of side-effects. Participants treated with dimethyl fumarate reported hot flushes (35, 33.7%) and intestinal side-effects (16, 15.4%) in almost identical frequency as stated in the official summary of the drug characteristics (Swissmedic, 2021). For teriflunomide, intestinal side-effects (4, 12.9%) and skin problems (5, 16.1%) were most often reported.

Although a more active disease may be the reason for starting or switching a therapy, based on real-world data from Switzerland, it has been shown that a burden-free life cannot necessarily be expected with a therapy duration of more than 6 months. On average, PwMS on DMT did not report the absence of symptoms. Our findings illustrate the complexity of the DMT decision making and the heterogeneity of the population of persons with RRMS with regards to the treatment effects, both desirable and undesirable. Treatment decisions need to integrate many factors such as symptom burden, DMT side-effect profiles, and personal preferences. Disease worsening and DMT switches due to side-effects are still relatively common events in the initial treatment phase. Of note, the relatively low percentages of such events observed in our study could be attributed the cross-sectional design. A longitudinal analysis would likely yield substantially higher cumulative incidence proportions (Spanu et al., 2020).

4.1. Strengths and limitations

A strength of our study is the diverse study population, which has been enrolled thanks to the innovative recruitment, and PwMS engagement approaches of the SMSR, which allows a cross-sectional analysis with a wide spectrum of diseases courses. While our study offers a precious insight into the perspectives of PwMS using self-reported data, it may suffer from recall or information bias. Furthermore, because current MS type was also based on self-reports, it is unclear whether a thorough clinical assessment would classify some participants as RRMS or as transitioning into secondary progressive MS. No potential confounders were considered in the present study. Further studies based on clinical data should be conducted either to validate our findings or to identify discrepancies between self-report and clinical data. With the data available, no conclusive statements can be made about the efficacy and safety profile of individual DMTs, nor on causality between self-reported side-effects and use of specific DMTs. This highlights the importance of longitudinal studies.

5. Conclusion

Our cross-sectional analysis of the real-world DMT situation suggests that, whilst the majority of persons with RRMS in Switzerland receive a *CONTINUED* treatment with seemingly tolerable DMT, there are still substantial subgroups that either receive no DMT (by choice or based on clinical criteria) or who grapple with possible side-effects and persistent disease worsening. The frequent self-reported side-effects of DMTs also warrant more attention. Even if there were no causal relationship with

Table 2
Socio-demographic and disease characteristics of persons with RRMS ($n = 416$), grouped by the five most frequently used DMT: Fingolimod, Dimethyl fumarate, Ocrelizumab, Natalizumab and Teriflunomide.

	Fingolimod	Dimethyl fumarate	Ocrelizumab	Natalizumab	Teriflunomide
Variable					
N	139 (33.4%)	104 (25.0%)	98 (23.6%)	44 (10.6%)	31 (7.5%)
Sex					
Male	37 (26.6%)	24 (23.1%)	26 (26.5%)	6 (13.6%)	2 (6.5%)
Female	102 (73.4%)	80 (76.9%)	72 (73.5%)	38 (86.4%)	29 (93.6%)
Language region					
German	128 (92.1%)	87 (83.7%)	77 (78.6%)	40 (90.9%)	21 (67.7%)
French	11 (7.9%)	16 (15.4%)	17 (17.4%)	2 (4.6%)	8 (25.8%)
Italian	0 (0.0%)	1 (1.0%)	4 (4.1%)	2 (4.6%)	2 (6.5%)
Age (mean, SD)	46.1 (9.9)	44.0 (11.5)	43.9 (11.9)	42.9 (11.9)	50.9 (9.8)
Age					
<50 years	87 (62.6%)	74 (71.2%)	67 (68.4%)	30 (68.2%)	15 (48.3%)
≥50 years	52 (37.4%)	30 (28.8%)	31 (31.6%)	14 (31.8%)	16 (51.6%)
DMT group					
CONTINUED treatment	132 (95.0%)	91 (87.5%)	75 (76.5%)	38 (86.4%)	27 (87.1%)
NEW treatment	7 (5.0%)	13 (12.5%)	23 (23.5%)	6 (13.6%)	4 (12.9%)
Relapse in the last 6 months					
No	123 (88.5%)	92 (88.5%)	87 (88.8%)	38 (86.4%)	28 (90.3%)
Yes	16 (11.5%)	12 (11.5%)	11 (11.2%)	6 (13.6%)	3 (9.7%)
Therapy discontinuation or interruption in the last 6 months					
No	138 (99.3%)	98 (94.2%)	88 (89.8%)	41 (93.2%)	30 (96.8%)
Yes	1 (0.7%)	6 (5.8%)	10 (10.2%)	3 (6.8%)	1 (3.2%)
Side-effect in the last 6 months					
No	115 (82.7%)	45 (43.3%)	76 (77.6%)	40 (90.9%)	19 (61.3%)
Yes	24 (16.3%)	59 (56.7%)	22 (22.5%)	4 (9.1%)	12 (38.7%)
Tiredness, Fatigue	7 (5.0%)	13 (12.5%)	12 (12.2%)	2 (4.5%)	4 (12.9%)
Hot flushes	3 (2.2%)	35 (33.7%)	3 (3.1%)	1 (2.3%)	1 (3.2%)
Others	6 (4.3%)	21 (20.2%)	8 (8.2%)	2 (4.5%)	2 (6.5%)
Headache	10 (7.2%)	6 (5.8%)	8 (8.2%)	1 (2.3%)	1 (3.2%)
Intestinal dysfunction, Digestive problems	3 (2.2%)	16 (15.4%)	4 (4.1%)	1 (2.3%)	4 (12.9%)
Skin problems	7 (5.0%)	12 (11.5%)	5 (5.1%)	0 (0.0%)	5 (16.1%)
Flu symptoms	1 (0.7%)	2 (1.9%)	6 (6.1%)	0 (0.0%)	1 (3.2%)
Pain	5 (3.6%)	2 (1.9%)	6 (6.1%)	1 (2.3%)	2 (6.5%)
Dizziness	4 (2.9%)	6 (5.8%)	5 (5.1%)	1 (2.3%)	1 (3.2%)
Sleeping problems, Insomnia	2 (1.4%)	4 (3.9%)	4 (4.1%)	1 (2.3%)	2 (6.5%)
Hair loss	2 (1.4%)	4 (3.9%)	4 (4.1%)	0 (0.0%)	2 (6.5%)
Allergic reaction	4 (2.9%)	5 (4.8%)	3 (3.1%)	0 (0.0%)	0 (0.0%)
Depression	1 (0.7%)	3 (2.9%)	5 (5.1%)	0 (0.0%)	0 (0.0%)
Opportunistic infection	2 (1.4%)	2 (1.9%)	1 (1.0%)	0 (0.0%)	3 (9.7%)
Manic or psychotic symptoms	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Measures to prevent PML	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Euphoria	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Time since diagnosis					
1–3 years	19 (13.7%)	28 (26.9%)	20 (20.4%)	4 (9.1%)	11 (35.5%)
4–10 years	67 (48.2%)	44 (42.3%)	41 (41.8%)	14 (31.8%)	9 (29.0%)
11–20 years	41 (29.5%)	25 (24.0%)	26 (26.5%)	19 (43.2%)	8 (25.8%)
21–30 years	10 (7.2%)	2 (1.9%)	10 (10.2%)	6 (13.6%)	2 (6.5%)
>30 years	0 (0.0%)	4 (3.9%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
Unknown	2 (1.4%)	1 (1.0%)	1 (1.0%)	1 (2.3%)	0 (0.0%)
Recently diagnosed, ≤3 years					
No	118 (84.9%)	75 (72.1%)	77 (78.6%)	39 (88.6%)	20 (64.5%)
Yes	19 (13.7%)	28 (27.0%)	20 (20.4%)	4 (9.1%)	11 (35.5%)
Unknown	2 (1.4%)	1 (1.0%)	1 (1.0%)	1 (2.3%)	0 (0.0%)
Number of symptoms in the last 6 months (mean, SD)	3.4 (4.1)	3.6 (4.3)	4.4 (4.9)	4.3 (4.4)	4.7 (4.0)
Number of symptoms in the last 6 months					
0	64 (46.0%)	43 (41.4%)	38 (38.8%)	17 (38.6%)	8 (25.8%)
1	6 (4.3%)	4 (3.9%)	2 (2.0%)	1 (2.3%)	0 (0.0%)
2–3	14 (10.1%)	15 (14.4%)	16 (16.3%)	3 (6.8%)	7 (22.6%)
4–5	12 (8.6%)	13 (12.5%)	7 (7.1%)	7 (15.9%)	4 (12.9%)
6–7	20 (14.4%)	9 (8.7%)	9 (9.2%)	4 (9.1%)	4 (12.9%)
8–9	12 (8.6%)	8 (7.7%)	5 (5.1%)	5 (11.4%)	3 (9.7%)
>9	11 (7.9%)	12 (11.5%)	21 (21.4%)	7 (9.1%)	5 (16.1%)
Symptoms in the last 6 months					
Tiredness, Fatigue	53 (38.1%)	48 (46.2%)	41 (41.8%)	21 (47.7%)	17 (54.8%)

(*continued on next page*)

Table 2 (*continued*)

	Fingolimod	Dimethyl fumarate	Ocrelizumab	Natalizumab	Teriflunomide
Paresthesia	50 (36.0%)	44 (42.3%)	43 (43.9%)	20 (45.5%)	17 (54.8%)
Pain	33 (23.7%)	22 (21.2%)	30 (30.6%)	18 (40.9%)	9 (29.0%)
Concentration problems	37 (26.6%)	26 (25.0%)	30 (30.6%)	11 (25.0%)	8 (25.8%)
Weakness	33 (23.7%)	15 (14.4%)	33 (33.7%)	13 (29.6%)	12 (38.7%)
Balance disorders	34 (24.5%)	22 (21.2%)	27 (27.6%)	14 (31.8%)	11 (35.5%)
Gait abnormalities	23 (16.6%)	19 (18.3%)	24 (24.5%)	14 (31.8%)	10 (32.3%)
Bladder disorders	25 (18.0%)	18 (17.3%)	21 (21.4%)	11 (25.0%)	7 (22.6%)
Spasms	15 (10.8%)	17 (16.4%)	21 (21.4%)	10 (22.7%)	8 (25.8%)
Dizziness	20 (14.4%)	23 (22.1%)	23 (23.5%)	8 (18.2%)	8 (25.8%)
Memory disorders	26 (18.7%)	21 (20.2%)	20 (20.4%)	7 (15.9%)	7 (22.6%)
Intestinal dysfunction	18 (13.0%)	17 (16.4%)	18 (18.4%)	9 (20.5%)	4 (12.9%)
Impaired vision	9 (9.5%)	17 (16.4%)	16 (16.3%)	4 (9.1%)	7 (22.6%)
Depression	14 (10.1%)	8 (7.7%)	17 (17.4%)	3 (6.8%)	2 (6.45%)
Sexual disorders	20 (14.4%)	7 (6.7%)	13 (13.3%)	10 (22.7%)	1 (3.2%)
Affective lability	8 (5.8%)	13 (12.5%)	9 (9.2%)	2 (4.6%)	3 (9.7%)
Tremor	11 (7.9%)	4 (3.9%)	11 (11.2%)	4 (9.1%)	2 (6.5%)
Language disorders	9 (9.5%)	12 (11.5%)	8 (8.2%)	3 (6.8%)	4 (12.9%)
Paralysis symptoms	10 (7.2%)	7 (6.7%)	7 (7.1%)	5 (11.4%)	1 (3.2%)
Twitching, Tics	7 (5.0%)	9 (8.7%)	5 (5.1%)	1 (2.3%)	2 (6.5%)
Dysphagia	5 (3.6%)	2 (1.9%)	6 (6.1%)	1 (2.3%)	2 (6.5%)
Problems with spatial orientation	5 (3.6%)	3 (2.9%)	5 (5.1%)	0 (0.0%)	2 (6.5%)
Others	1 (0.7%)	3 (2.9%)	1 (10.2%)	0 (0.0%)	0 (0.0%)
Epileptic seizure	1 (0.7%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Number of different DMTs used, including current (mean, SD)	1.7 (0.9)	1.7 (0.9)	2.4 (1.3)	2.3 (1.1)	1.9 (1.2)
Number of different DMTs used, including current					
1	72 (51.8%)	57 (54.8%)	31 (31.6%)	10 (22.7%)	16 (51.6%)
>1	67 (48.2%)	47 (45.2%)	67 (68.4%)	34 (77.3%)	15 (48.4%)
Number of non-pharmacological and alternative medical treatments in the last 6 months (mean, SD)	1.2 (1.6)	1.4 (1.9)	1.2 (1.8)	1.3 (1.6)	0.8 (1.8)
Non-pharmacological and alternative medical treatments in the last 6 months					
Other vitamin and mineral supplements	37 (26.6%)	31 (29.8%)	22 (22.4%)	12 (27.3%)	4 (12.9%)
Physiotherapy	26 (18.7%)	18 (17.3%)	23 (23.5%)	11 (25.0%)	6 (19.4%)
Vitamin B supplements	22 (15.8%)	18 (17.3%)	10 (10.2%)	8 (18.2%)	2 (6.5%)
Others	23 (16.5%)	11 (10.6%)	12 (12.2%)	7 (15.9%)	1 (3.2%)
Relaxation therapies	16 (11.5%)	12 (11.5%)	8 (8.2%)	2 (4.5%)	3 (9.7%)
Naturopathy	7 (5.0%)	12 (11.5%)	9 (9.2%)	4 (9.1%)	3 (9.7%)
Osteopathy	7 (5.0%)	8 (7.7%)	2 (2.0%)	4 (9.1%)	2 (6.5%)
Homeopathy	6 (4.3%)	6 (5.8%)	7 (7.1%)	2 (4.5%)	0 (0.0%)
Psychotherapy	9 (6.5%)	5 (4.8%)	6 (6.1%)	3 (6.8%)	1 (3.2%)
Acupuncture	10 (7.2%)	6 (5.8%)	3 (3.1%)	2 (4.5%)	0 (0.0%)
Occupational therapy	1 (0.7%)	2 (1.9%)	3 (3.1%)	1 (2.3%)	1 (3.2%)
Cranberry juice	1 (0.7%)	4 (3.8%)	1 (1.0%)	1 (2.3%)	0 (0.0%)
Nutritional therapy	3 (2.2%)	1 (1.0%)	5 (5.1%)	1 (2.3%)	0 (0.0%)
Hippotherapy	2 (1.4%)	4 (3.8%)	1 (1.0%)	0 (0.0%)	1 (3.2%)
Aromatherapy	0 (0.0%)	3 (2.9%)	2 (2.0%)	0 (0.0%)	0 (0.0%)
Trigger point therapy	0 (0.0%)	3 (2.9%)	2 (2.0%)	0 (0.0%)	1 (3.2%)
Neuropsychological therapy	0 (0.0%)	1 (1.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)
Speech and language therapy	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
SRDSS					
0–3.5	132 (95.0%)	99 (95.2%)	82 (83.7%)	41 (93.2%)	28 (90.3%)
4–6.5	6 (4.3%)	2 (1.9%)	12 (12.2%)	3 (6.8%)	2 (6.5%)
7–9.5	0 (0.0%)	2 (1.9%)	4 (4.1%)	0 (0.0%)	0 (0.0%)
Unknown	1 (0.7%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
Comorbidity					
No	105 (75.5%)	87 (83.7%)	77 (78.6%)	40 (90.9%)	27 (87.1%)
Yes	33 (23.7%)	16 (15.4%)	21 (21.4%)	4 (9.1%)	4 (12.9%)
Unknown	1 (0.7%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MFIStotal (mean, SD)	26.4 (17.7)	23.3 (17.6)	30.5 (21.5)	28.2 (20.8)	28.3 (21.6)
MFIS clinically relevant, ≥38					
No	102 (73.4%)	78 (75.0%)	58 (59.2%)	26 (59.1%)	19 (61.3%)
Yes	32 (23.0%)	24 (23.1%)	34 (24.7%)	17 (38.6%)	9 (29.0%)
Unknown	5 (3.6%)	2 (1.9%)	6 (6.1%)	1 (2.3%)	3 (9.7%)
EQ-5D-Index, scaled to 0–100 (mean, SD)	83.9 (14.0)	86.6 (13.8)	80.9 (15.8)	80.2 (16.2)	79.7 (14.8)
VAS (mean, SD)	81.3 (16.2)	83.2 (15.2)	76.9 (19.2)	77.8 (16.3)	74.7 (24.9)
VAS					
0–25	2 (1.4%)	0 (0.0%)	3 (3.1%)	0 (0.0%)	2 (6.5%)
26–50	6 (4.3%)	8 (7.7%)	13 (13.3%)	3 (6.8%)	4 (12.9%)
51–75	34 (24.5%)	17 (16.4%)	19 (19.4%)	15 (34.1%)	6 (19.4%)
76–100	97 (69.8%)	79 (76.0%)	63 (64.3%)	26 (59.1%)	19 (61.3%)

DMTs, these symptoms would point to a need for clarifications of DMT characteristics (including known side-effects) and expectations of PwMS with respect to treatment outcomes.

Funding

The Swiss MS Registry (SMSR) is funded by the Swiss Multiple Sclerosis Society. The funding source had no role in the study design; collection, analysis, management, and interpretation of the data; writing of the report or decision to submit the manuscript for publication.

Supporting information

supp

CRediT authorship contribution statement

Jonas Bossart: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing – original draft, Visualization, Project administration. **Christian P. Kamm:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – original draft, Writing – review & editing. **Marco Kaufmann:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Mina Stanikić:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Milo A. Puhan:** Investigation, Resources, Writing – review & editing, Supervision, Funding acquisition. **Jürg Kesselring:** Investigation, Resources, Writing – review & editing. **Chiara Zecca:** Investigation, Resources, Writing – review & editing. **Claudio Gobbi:** Investigation, Resources, Writing – review & editing. **Irene Rapold:** Investigation, Resources, Writing – review & editing. **Roland Kurmann:** Investigation, Resources, Writing – review & editing. **Sabin Ammann:** Data curation. **Viktor von Wyl:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

CPK has received honoraria for lectures as well as research support from Biogen, Novartis, Almirall, Teva, Merck, Sanofi Genzyme, Roche, Janssen, Eli Lilly, Celgene and the Swiss MS Society (SMSG).

MS reports employment by Roche branch in Serbia, Roche d.o.o., from February 2019 to February 2020.

CZ and CG The Employer Department of Neurology, Regional Hospital Lugano (EOC), Lugano, Switzerland receives financial support for speaking, educational, research or travel grants from Abbvie, Almirall, Biogen Idec, Celgene, Sanofi, Merck, Novartis, Teva Pharma, Roche.

JB, MK, MAP, JK, IR, RK SA, and VvW declare no conflict of interest.

Acknowledgments

We would like to express our special thanks to the participants in the study, whose help and participation in the SMSR surveys made this analysis possible. Our gratitude further goes to the Swiss Multiple Sclerosis Society for funding the Registry, as well as to the Medico-Scientific Advisory Board of the Swiss Multiple Sclerosis Society for their support. We would also like to thank the members of the SMSR at the Institute of Epidemiology, Biostatistics and Prevention of the University of Zurich for their support, namely Gabor Horvath for providing the data, and Stephanie Rodgers for her advice regarding MFIS.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103706.

References

Brancati, S., Gozzo, L., Longo, L., Vitale, D.C., Drago, F., 2021. Rituximab in multiple sclerosis: are we ready for regulatory approval? Front. Immunol. 12 https://doi.org/10.3389/fimmu.2021.661882.

Braune, S., Rossnagel, F., Dikow, H., Bergmann, A., 2021. Impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany between 2010 and 2018: real-world data from the German NeuroTransData multiple sclerosis registry. BMJ Open 11. https://doi.org/10.1136/bmjopen-2020-042480.

Brooks, R., 1996. The current state of play. Health Policy 37, 53–72. New. York.

Coret, F., Pérez-Miralles, F.C., Gascón, F., Alcalá, C., Navarré, A., Bernad, A., Boscá, I., Escutia, M., Gil-Perotin, S., Casanova, B., 2018. Onset of secondary progressive multiple sclerosis is not influenced by current relapsing multiple sclerosis therapies. Mult. Scler. J. Exp. Transl. Clin. https://doi.org/10.1177/2055217318783347. April.

EuroQol, R., 1990. EuroQol–a new facility for measurement of health-related quality of life. Health Policy 16, 199–208. New York(New. York).

Farley, S., Gottesman, M.H., Friedman-Urevich, S., Ye, J., Shen, M., Grueneberg, D., Martone, L., Calixte, R., 2019. Anti-John Cunningham virus antibody index levels in multiple sclerosis patients treated with rituximab, fingolimod, and dimethyl fumarate. Surg. Neurol. Int. 10 https://doi.org/10.25259/SNI-4-2019.

Fischer, J.S., LaRocca, N.G., Miller, D.M., Ritvo, P.G., Andrews, H., Paty, D., 1999. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult. Scler. 5, 251–259. https://doi.org/10.1177/135245859900500410.

Flachenecker, P., Kümpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., Trenkwalder, C., Toyka, K.V., 2002. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult. Scler. J. 8, 523–526. https://doi.org/10.1191/1352458502ms839oa.

Jalkh, G., Abi Nahed, R., Macaron, G., Rensel, M., 2021. Safety of newer disease modifying therapies in multiple sclerosis. Vaccines 9. https://doi.org/10.3390/vaccines9010012. Basel.

Kaufmann, M., Salmen, A., Barin, L., Puhan, M.A., Calabrese, P., Kamm, C.P., Gobbi, C., Kuhle, J., Manjaly, Z.M., Ajdacic-Gross, V., Schafroth, S., Bottignole, B., Ammann, S., Zecca, C., D'Souza, M., von Wyl, V., 2020. Development and validation of the self-reported disability status scale (SRDSS) to estimate EDSS-categories. Mult. Scler. Relat. Disord. 42 https://doi.org/10.1016/j.msard.2020.102148.

Khatri, B.O., 2016. Fingolimod in the treatment of relapsing-remitting multiple sclerosis: long-term experience and an update on the clinical evidence. Ther. Adv. Neurol. Disord. 9, 130–147. https://doi.org/10.1177/1756285616628766.

Learmonth, Y.C., Dlugonski, D., Pilutti, L.A., Sandroff, B.M., Klaren, R., Motl, R.W., 2013. Psychometric properties of the fatigue severity scale and the modified fatigue impact scale. J. Neurol. Sci. 331, 102–107. https://doi.org/10.1016/j.jns.2013.05.023.

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournaoeau, D., Brucher, M., Perrot, M., Duchesnay, É., 2011. Scikit-learn: machine leraning in python. J. Mach. Learn. Res. 12, 2825–2830. https://doi.org/10.1145/2786984.2786995.

Puhan, M., Steinemann, N., Kamm, C., Müller, S., Kuhle, J., Kurmann, R., Calabrese, P., Kesselring, J., von Wyl, V., 2018. A digitally facilitated citizen-science driven approach accelerates participant recruitment and increases study population diversity. Swiss Med. Wkly. 148 https://doi.org/10.4414/smw.2018.14623.

Rabin, R., De Charro, F., 2001. EQ-5D: a measure of health status from the EuroQol group. Ann. Med. 33, 337–343. https://doi.org/10.3109/07853890109002087.

Rempe, T., Carlson, A., Miravalle, A., Gyang, T.V., 2020. Anti-JCV antibody index does not change during ocrelizumab-treatment. Mult. Scler. J. Exp. Transl. Clin. 6 https://doi.org/10.1177/2055217320960510.

Rubin, D.B., 1996. Multiple Imputation after 18^{+} years. J. Am. Stat. Assoc. 91, 473–489. https://doi.org/10.1080/01621459.1996.10476908.

Spanu, A., Aschmann, H.E., Kesselring, J., Puhan, M.A., 2020. Benefit-harm balance of fingolimod in patients with MS: a modelling study based on FREEDOMS. Mult. Scler. Relat. Disord. 46 https://doi.org/10.1016/j.msard.2020.102464.

Spelman, T., Magyari, M., Piehl, F., Svenningsson, A., Rasmussen, P.V., Kant, M., Sellebjerg, F., Joensen, H., Hillert, J., Lycke, J., 2021. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2021.2738.

Steinemann, N., Kuhle, J., Calabrese, P., Kesselring, J., Disanto, G., Merkler, D., Pot, C., Ajdacic-Gross, V., Rodgers, S., Puhan, M.A., von Wyl, V., 2018. The Swiss multiple sclerosis registry (SMSR): study protocol of a participatory, nationwide registry to promote epidemiological and patient-centered MS research. BMC Neurol. 18 https://doi.org/10.1186/s12883-018-1118-0.

Tanasescu, R., Ionete, C., Chou, I.J., Constantinescu, C.S., 2014. Advances in the treatment of relapsing-remitting multiple sclerosis. Biomed. J. 37, 41–49. https://doi.org/10.4103/2319-4170.130440.

The Council, 1998. Guidelines MSCfCP: Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis: clinical practice guidelines. Paralyzed Veterans of America, Washington D.C.

Turčáni, P., Mašková, J., Húska, J., 2020. 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. Patient Prefer. Adherence 14, 1129–1135. https://doi.org/10.2147/PPA.S254427.

Van Rossum, G., Drake, F.L., 2009. Python 3 Reference Manual. CreateSpace, Scotts Valley, CA.

Wingerchuk, D.M., Carter, J.L., 2014. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin. Proc. 89, 225–240. https://doi.org/10.1016/j.mayocp.2013.11.002.

Zadeh, A.R., Ghadimi, K., Ataei, A., Askari, M., Sheikhinia, N., Tavoosi, N., Falahatian, M., 2019. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. Int. J. Physiol. Pathophysiol. Pharmacol. 11, 105–114.

Zeydan, B., Kantarci, O.H., 2020. Impact of age on multiple sclerosis disease activity and progression. Curr. Neurol. Neurosci. Rep. 20 https://doi.org/10.1007/s11910-020-01046-2.

Swissmedic, 2021. Arzneimittelinformation. https://www.swissmedicinfo.ch/ (accessed 18 August 2021).