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MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry

Multiple Sclerosis Journal

2019, Vol. 25(12) 1641–1652

DOI: 10.1177/1352458518799580

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Paulus Stefan Rommer, Kerstin Eichstädt, David Ellenberger, Peter Flachenecker, Tim Friede, Judith Haas, Christoph Kleinschnitz, Dieter Pöhlau, Otto Rienhoff, Alexander Stahmann and Uwe Klaus Zettl

Abstract

Background: Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease. Over time, symptoms accumulate leading to increased disability of patients.

Objective: The objective of this article is to analyze the prevalence of symptoms and symptomatic treatment patterns in a nationwide MS registry.

Methods: Data sets from 35,755 patients were analyzed.

Results: More than two-thirds of patients were women with a mean age of 46.1 (±12.8) years. Median Expanded Disability Status Score (EDSS) was 3.0. The most frequently reported symptoms were fatigue, spasticity, and voiding disorders. In patients with short disease duration, fatigue was reported most frequently. Symptomatic treatment was most common for spasticity and depression, whereas fatigue was treated only in a third of affected patients. Almost a fifth of patients with EDSS ⩽ 3.5 and neuropsychological symptoms had retired from work.

Conclusion: Whereas treatment for spasticity and depression is common in our cohort, sexual dysfunction, dysphagia, cognitive dysfunction, and fatigue are treated to a far lesser extent. The need for psychological support, physical, and occupational therapy has to be recognized as neuropsychological symptoms have a great impact on retirement at an early stage. Overall symptomatic treatment rates for the most common symptoms have increased over the last years ($p < 0.001$).

Keywords: Multiple sclerosis, symptoms, symptomatic treatment, symptom manifestation, disability progression

Date received: 10 March 2018; revised: 1 August 2018; accepted: 9 August 2018

Correspondence to:
PS Rommer
Department of Neurology, Neuroimmunological Section, University of Rostock, Gehlsheimer Straße 20, 18147 Rostock, Germany.
stefan.rommer@med.uni-rostock.de

Paulus Stefan Rommer
Department of Neurology, Neuroimmunological Section, University of Rostock, Rostock, Germany/ Department of Neurology, Medical University of Vienna, Vienna, Austria

Kerstin Eichstädt
MS Forschungs- und Projektentwicklungs-gGmbH, Hannover, Germany

David Ellenberger
Department of Medical Statistics, University Medical Centre Göttingen, Göttingen, Germany

Peter Flachenecker
Neurological Rehabilitation Center Quellenhof, Bad Wildbad, Germany

Tim Friede
Department of Medical Statistics, University Medical Centre Göttingen, Göttingen, Germany

Judith Haas
MS-Center, Jewish Hospital Berlin, Berlin, Germany

Christoph Kleinschnitz
Department of Neurology, University Hospital Essen, Essen, Germany

Dieter Pöhlau
Department of Neurology, German Red Cross—Kamillus-Clinic, Asbach, Germany

Otto Rienhoff
Department of Medical Informatics, University Medical Center Göttingen, Göttingen, Germany

Introduction

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease of the central nervous system (CNS) that can cause substantial disability.[1,2] There are more than 200,000 patients in Germany[3] and approximately 2.3 million worldwide.[4] A relapsing course with acute attacks leading to new symptoms or deterioration of pre-existing symptoms can be distinguished from a progressive course, defined as continuous deterioration of overall function.[5] Symptoms include mobility restrictions oftentimes due to paresis and spasticity, visual impairment, bladder and bowel problems, sexual dysfunction, pain, depression, cognitive deficits and fatigue.[6,7] Treatment of MS aims at (1) ameliorating relapses with high-dose glucocorticosteroids, (2) influencing the disease course by reducing relapse rates and delaying progression during an until now unknown time period with immunomodulatory/immunosuppressive agents, and (3) improving activities of daily living and increasing the well-being of patients by symptomatic treatment.[8,9]

The German MS Registry collects and provides data from MS patients with regard to disease characteristics, treatment, and health care use.[6,10] Based on the data, an analysis was performed in 2009 to illuminate the prevalence and treatment of MS-related symptoms.[10] Since that report, renewed therapeutic guidelines and a modified therapy landscape have led to improved care. The aim of this analysis is to provide a follow-up of the evaluation in light of this progress.

Alexander Stahmann
MS Forschungs- und Projektentwicklungs-gGmbH, Hannover, Germany

Uwe K laus Zettl
Department of Neurology, Neuroimmunological Section, University of Rostock, Rostock, Germany

Patients and methods

The German MS Registry

The German MS Registry is a national project which was initiated in 2001 by the German MS Society (DMSG, Bundesverband e.V.) and has been described previously in detail.[11]

For participating centers, data collected during routine practice were entered electronically using the Multiple Sclerosis Documentation System software via an additional module implementing the export of the standardized minimal data set (https://www.dmsg.de/msregister/download/nextCloud/index.php/s/sy3xTEX2Myqs9B4).[12]

Criteria for data extraction

All data were checked with an extensive quality control ruleset to guarantee completeness of mandatory data and consistency of all data sets. Questionable or incomplete data were routinely reported to the centers for correction, annotation, or completion. Only complete (with regard to the minimal data set), non-questionable, or annotated data from centers complying with the documentation standards set up by the MS Registry group were included in the analysis. All data completeness and quality checks were implemented in the SPSS command syntax language that allows a reproducible data pool to be generated.

Inclusion criteria

The inclusion criteria for the MS registry were as follows:

1. A diagnosis of MS (according to McDonald or Poser et al. criteria[13,14]) or a clinically isolated syndrome;
2. Primary residency in Germany;
3. Written informed consent from patients for participation.

Analysis was performed using data sets of all patients who have been enrolled in the registry since 2001. These patients represent the full data set (see Figure 1). With regard to single analyses, patients with missing information or unknown status were deducted from the full data set, and only patients with information on respective symptoms were evaluated. To enable a comparison with our previous analysis,[6] we limited our analysis to patients for whom an updated data set (all data sets since 2010) is present in the registry. Patients' birth date, sex, first recorded MS type (relapsing onset, progressive onset), date of symptom onset, symptoms at onset, current MS disease course, current symptoms, current disease progression (according to the Expanded Disability Status Score (EDSS)), and work status were extracted.

Statistical analysis

Descriptive statistics include frequencies for categorical responses and means and standard error of the mean (SEMs) for continuous outcomes. The comparisons of frequencies of initial symptoms and treatments between patients with relapsing onset of MS (ROMS—comprising relapsing and secondary progressive MS (SPMS)) and primary progressive MS (PPMS) were assessed with risk ratios and chi-square tests. The comparisons of age of onset were done with kernel density estimates (Epanechnikov), including bootstrap confidence intervals (CIs) and Welch's *t*-test as a global test for differences. General additive models with thin plate regression splines were used to model the possible non-linear effects of the age of onset on the frequency of symptoms. We did not adjust *p* values for multiple testing due to the exploratory nature of the study and considered *p* values smaller than 1% as statistically significant.

Data transformation and statistical analyses were performed with R 3.3.1 (R Foundation, Vienna, Austria).

Ethics

All data were collected in accordance with the Declaration of Helsinki, and the registry received ethical approval, for example, by the independent ethics committee at the University of Würzburg. All patients in the registry gave their written informed consent. The registry is listed at the German registry of clinical trials under the registration number DRKS00011257. To guarantee the privacy of patients, only de-identified data sets were transferred from the centers to the MS Forschungs- und Projektentwicklungs-gGmbH (MSFP); the conduct of the registry was approved by the respective data protection authorities.

Results

Since 2001, data sets of 47,967 patients passed the quality control of the registry and were considered for analyses. In the present analysis, we included the data sets of all patients that were updated since the interim analysis[11] until June 2016. Thus, a subset of 35,755 patients from 148 centers was available for this study. As only data sets with information on the respective symptoms were assessed, the numbers of analyzed patients differ for the various symptoms.

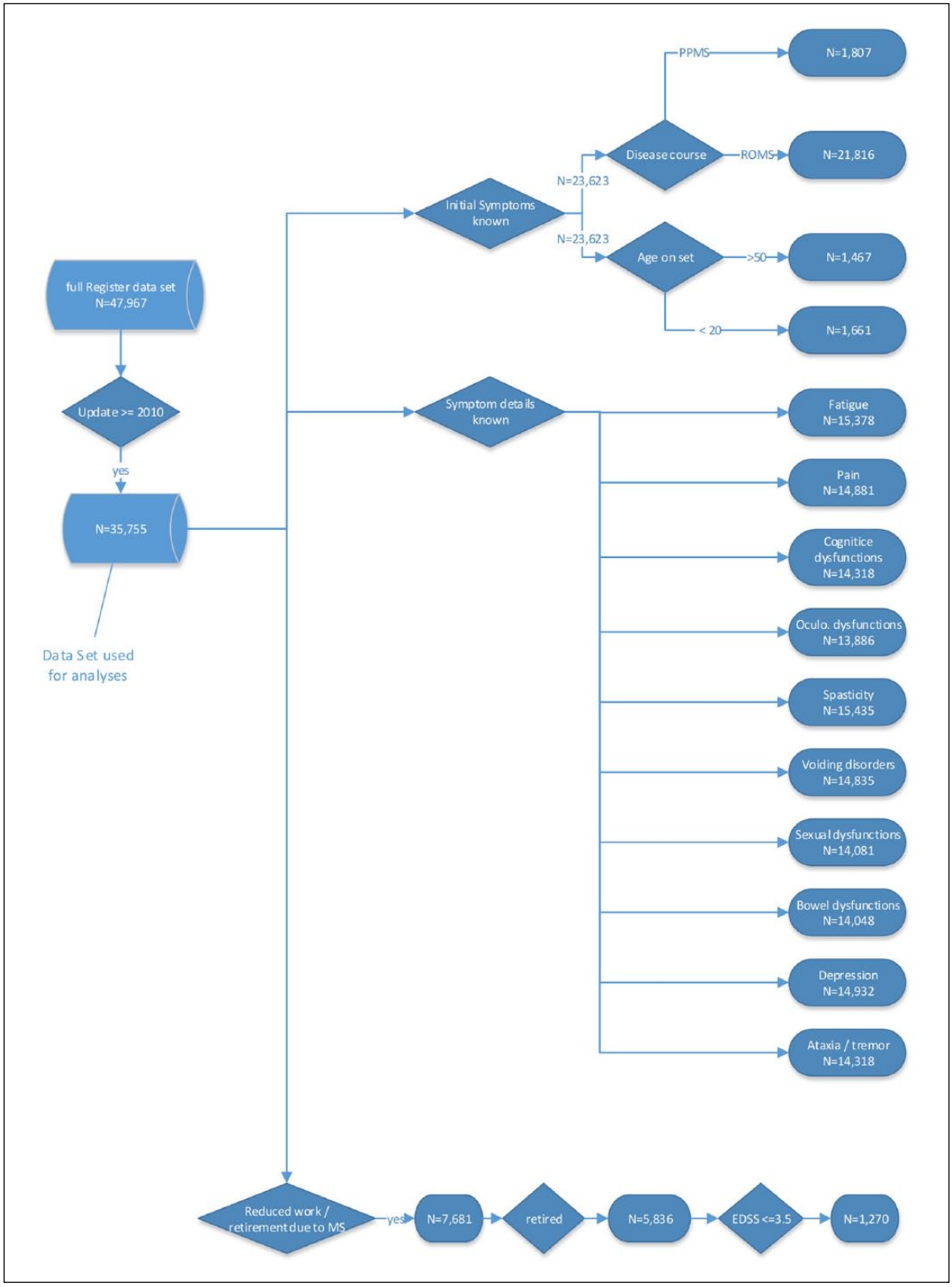

Figure 1. Flowchart of the full registry data set, broken down by various research questions.

Table 1. Demographics of patients included in the study.

	n	Mean age (years; ±SEM)	Mean disease duration (years; ±SEM)	EDSS median	Female (%)
MS	35,755	46.13 ± 12.2	12.8 ± 9.8	3	70.9
RRMS	21,261	42.77 ± 10.9	10.7 ± 8.0	2	73.1
SPMS	7,803	52.2 ± 10.1	21.0 ± 9.8	6	68.2
PPMS	2,289	56.2 ± 10.5	14.7 ± 9.9	5.5	58.5
Unclassified	2,681	38.1 ± 11.4	2.7 ± 3.6	1.5	69.5

SEM: standard error of mean; EDSS: Expanded Disability Status Score; MS: multiple sclerosis; RRMS: relapsing–remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS.
For 1,721 patients, no disease course was available.

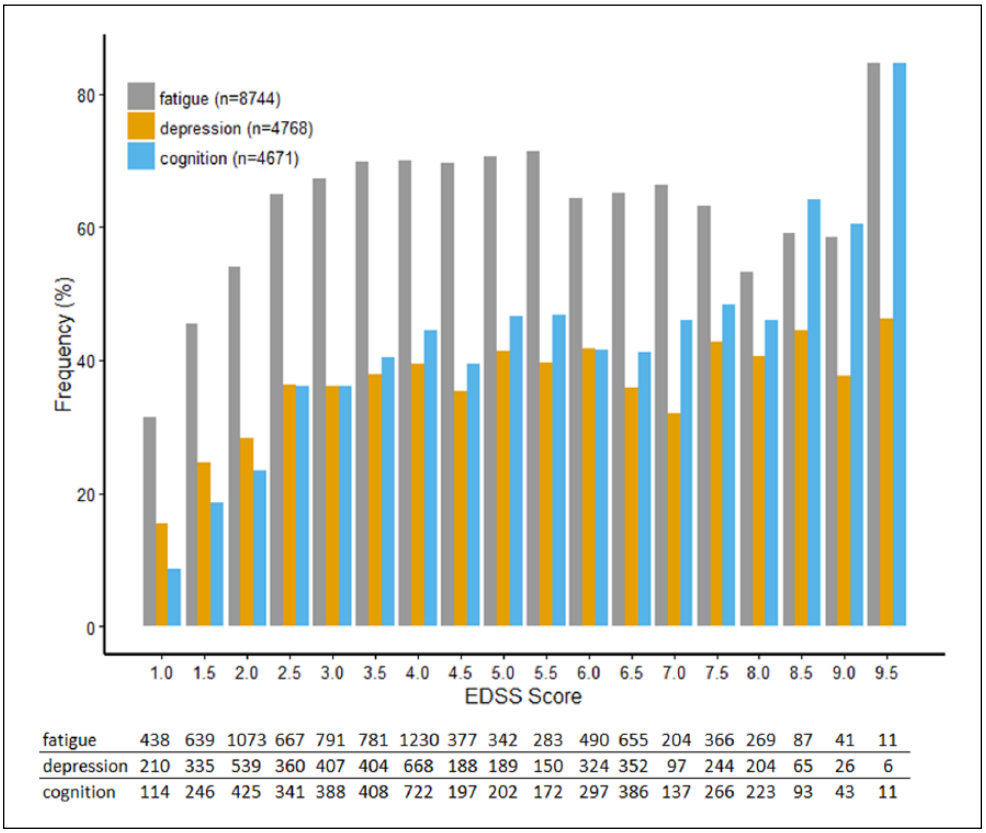

Figure 2. Frequency of neuropsychological and emotional symptoms (cognition, fatigue, and depression) according to disability as measured by Expanded Disability Status Score (EDSS).

More than two-thirds of the enrolled patients were women (70.9%), mean (±standard deviation) age of analyzed patients was 46.1 (±12.8) years, mean age of onset for relapsing–remitting MS (RRMS) patients was 32.2 (±9.9) years and 41.6 (±11.0) years for PPMS patients, and mean disease duration was 12.8 (±9.8) years. Overall, 21,260 patients suffered from an RRMS (59.5%). The median EDSS was 3.0; 7298 patients (20.4%) had an EDSS of 6.0 or higher (see Table 1).

In 7681 patients (21.5%), MS-associated disability led to occupational changes (e.g. retraining measures, retirement), and one out of four patients (24.7%) had prematurely retired from work due to MS. Overall retirement rate in our cohort was 29.4% (see Figure 1). Prevalence of fatigue, depression and cognitive disorders was high in patients with EDSS ⩽3.5 (see Figure 2), and in those patients, retirement rates were 16.7% for patients with fatigue, 19.4% for patients with depression, and 21.2% for patients with

Table 2. Initial symptoms reported by the patients and recorded by the investigators (sorted by frequency).

Symptom	MS	RRMS (at onset)	PPMS	*p* value*	Risk ratio
Number	25,858	21,816	1,807		
Dysesthesia	47.4%	48.4%	30.1%	<0.001	1.61
Paresis	37.1%	35.8%	64.0%	<0.001	0.56
Optic neuritis	29.0%	30.7%	12.8%	<0.001	2.40
Balance disorders	24.6%	24.3%	32.7%	<0.001	0.74
Cranial nerves	13.8%	14.4%	8.9%	<0.001	1.62
Fatigue	9.8%	9.7%	11.0%	0.07	0.88
Voiding disorders	6.8%	6.7%	11.8%	<0.001	0.57
Depression	3.2%	3.2%	3.9%	0.11	0.82

SEM: standard error of mean; EDSS: Expanded Disability Status Score; MS: multiple sclerosis; RRMS: relapsing–remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS.
*Done with Pearson's chi-square test.

cognitive dysfunction and increased with EDSS (see supplemental Table 1).

Initial symptoms

A polysymptomatic onset was recorded in 44.1% of the patients. Most common initial symptoms were dysesthesia in 47.4% of the patients, followed by paresis (37.1%) and visual problems, for example, optic neuritis (29.0%); 24.6% of the patients reported balance problems.

RRMS patients ($n=21,816$) presented most often with dysesthesias (48.4%), followed by paresis (35.8%) and optic neuritis (30.7%), whereas in PPMS patients ($n=1807$), the leading symptom was paresis (64.0%) followed by balance problems in 32.7%. A significant difference was reported in the occurrence of most of the initial symptoms for RRMS and PPMS patients ($p<0.001$; see Table 2 and Figure 3).

Symptoms over the course of the disease

The most frequently reported symptom independently from disease course was fatigue, with a prevalence of 58.1%, followed by spasticity (47.5%), voiding disorders (44.0%), ataxia/tremor (35.7%), pain (34.2%), cognitive impairment (33.0%), and depression (32.5%).

In patients with disease duration of less than 2 years, fatigue was the most reported symptom (31.0%), followed by bowel dysfunction (29.4%), depression (15.9%), pain (15.6%), and cognition problems (14.8%).

Fatigue was the most reported symptom (57.6%) in RRMS patients, whereas the most frequent symptom in SPMS and PPMS patients was spasticity (81.9% and 74.2%, respectively). Whereas voiding disorders were seen in 72.9% of patients suffering from SPMS, and in 61.8% of PPMS patients, they were less frequently reported in RRMS patients (31.3%). Similarly, ataxia/tremor and sexual dysfunction were more common in progressive MS (SPMS and PPMS) than in RRMS with respective prevalence of 56.7%, 49.8%, and 26.8% (SPMS, PPMS, and RRMS) for ataxia/tremor and 20.0%, 18.4%, and 9.5% (SPMS, PPMS, and RRMS) for sexual dysfunctions (see supplemental Table 2).

Treatment of symptoms

Symptomatic treatment comprised pharmacological (drug) therapy and non-pharmacological treatment or a combination of both (Table 3). Prevalence of treatment differed between various symptoms and was most commonly administered in epilepsy (79.8%, not shown in Table 3), spasticity (78.0%), depression (74.5%), and pain (74.9%). Although fatigue was the most common symptom (58.1%), treatment was only given in 34.8% of the patients. Similarly, dysarthria (not shown in Table 3), dysphagia (not shown in Table 3), cognitive disorders, sexual dysfunction, and dysfunctions of the oculomotor system were treated in the minority of the patients (respective numbers are 36.0%, 30.4%, 27.0%, 21.2%, and 20.9%).

Treatment patterns varied between symptoms, with solely pharmacological treatment for epilepsy (77.2%), depression (59.6%), and pain (57.1%) in a majority of patients and solely non-pharmacological treatment to a higher extent for ataxia (45.8%), dysphagia (26.0%), dysarthria (25.5%), spasticity (25.2%), and cognitive dysfunctions (22.1%). Combination treatment was most common for spasticity (19.0%).

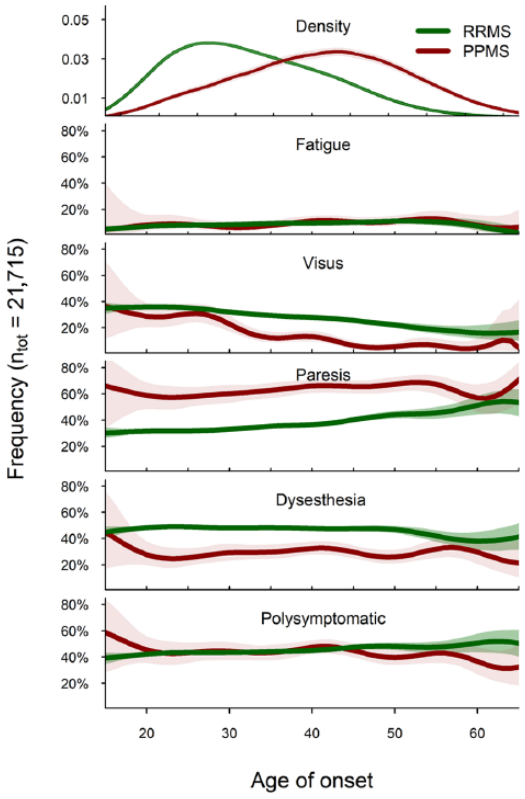

Figure 3. The upper graph shows the age of onset for patients with relapsing–remitting multiple sclerosis (RRMS, green lines) and with primary progressive multiple sclerosis (PPMS, red lines). The lower graphs show the frequency of the respective initial symptoms as a function of age of onset for both disease courses estimated by generalized additive models. Statistics: comparisons of age of onset were done with kernel density estimates (Epanechnikov), including bootstrap CIs and Welch's *t*-test as a global test for differences. General additive models with thin plate regression splines were used to model the possible non-linear effects of the age of onset on the frequency of symptoms; 95% CI are presented as color-shaded areas.

With regard to non-pharmacological treatment, physical therapy was the most common non-pharmacological treatment overall (84.2%) and especially in spasticity (97.0%), ataxia/tremor (97.0%), cognitive dysfunction (94.7%), voiding disorders (96.0%), fatigue (93.6%), and depression (90.7%). Occupational therapy was reported in a 43.3% of the enrolled patients, psychotherapy in 23.4% of the patients, and neuropsychological training in 17.7% of the patients; 71.3% of the patients with depression received psychotherapy. Besides physical therapy, occupational therapy, neuropsychological training, and psychotherapy were often offered to patients with cognitive dysfunction (respective numbers are 75.1%, 47.3%, and 40.4%).

Discussion

With more than 35.000 analyzed patients, our study is one of the largest on MS symptomatology. One major focus was on neuropsychological symptoms such as fatigue, depression, and cognition that already persist at an early stage in our cohort; 31% of patients complained of fatigue within the first 2 years of disease, which is the most common symptom at the early stage of disease, followed by depression. Interestingly, this has not been reported in key studies over the last decades.[15–18] Fatigue is an unspecific symptom that is not clinically overt and may thus not always ascribed to MS.[19] Over the last years, these soft or hidden symptoms are considered to be highly important.[20] Neuropsychological symptoms are not always obvious on clinical examination and clinical scales (see Figure 2), and especially for fatigue, overlapping causes (cognitive fatigue, motor fatigue, depression, side effects of therapeutic agents, and sleep disturbances) may complicate diagnosis and treatment.[19]

As a consequence, fatigue and cognitive dysfunctions are only treated insufficiently in patients. In contrast, depression, spasticity, pain, and epilepsy are treated to a much higher extent (up to 80% of affected patients). These differences are partly explained by the availability of treatment options that can be either pharmacological or non-pharmacological. Whereas treatment for depression is mainly based on medication, non-pharmacological interventions are primarily utilized in patients with ataxia/tremor, dysphagia, and dysarthria. Treatment of spasticity comprises both options in many individuals. The low percentages of treated patients with fatigue and cognitive dysfunction may reflect limited treatment options.[21] In addition, peculiarities in the patient–physician relationship, complex interactions with other symptoms, for example, fatigue or depression, and little awareness of symptoms might influence treatment patterns, for example, for sexual dysfunction.[22–24] Together with statistical reasons, the low number of reported patients in this symptom might, partly, explain why only one of seven patients with reported sexual dysfunctions received treatment in our patient cohort. Non-pharmacological treatment was given for symptoms with limited pharmacological treatment options. Physical activity and occupational therapy have shown positive impacts on cognition and other neuropsychological symptoms in MS patients.[25,26] Physical therapy was the most common non-pharmacological intervention for patients

Table 3. Pharmacological and non-pharmacological treatment of symptoms (sorted by change and only the most frequent symptoms are reported).

Symptom	2001–2009 (Skierlo et al.)					2010–2015					Change (±) (%)	*p* value*
	n	NT (%)	P (%)	NP (%)	PNP (%)	*n*	NT (%)	P (%)	NP (%)	PNP (%)		
Depression	1,534	41.1	48.8	8.4	1.7	4,853	25.5	59.6	10.7	4.3	+15.6	<0.001
Pain	1,635	39.3	47.0	10.1	3.5	5,084	26.1	57.1	9.9	6.9	+13.2	<0.001
Ataxia/tremor	2,159	56.1	8.7	33.4	1.8	5,110	43,8	8.7	45.8	1.7	+12.3	<0.001
Spasticity	2,686	31.5	33.8	21.1	13.7	7,332	22.0	36.5	22.5	19.0	+9.5	<0.001
Fatigue	2,991	76.2	12.0	11.3	0.5	8,932	65.2	14.9	18.2	1.7	+9.0	<0.001
Cognitive dysfunctions	1,653	80.8	5.4	13.1	0.7	4,723	73.0	3.9	22.1	0.9	+7.8	<0.001
Voiding disorders	2,641	50.9	30.8	14.0	4.3	6,527	44.7	31.5	17.6	6.2	+6.2	<0.001
Dysfunction of the oculomotor system	968	84.4	7.5	8.1	0	2,175	79.1	11.1	9.4	0.4	+5.3	<0.001
Bowel dysfunctions	933	54.1	30.3	13.9	1.6	1,960	50.6	31.6	15.1	2.8	+3.5	0.08
Sexual dysfunctions	757	84.0	10.0	4.8	1.2	1,782	78.8	13.4	6.3	1.5	+5.2	0.003

n: number; NT: no treatment; P: pharmacological therapy; NP: non-pharmacological therapy; PNP: combination of pharmacological and non-pharmacological therapy.
*Done with Pearson's chi-square test.

with cognitive problems, fatigue, voiding disorders, ataxia/tremor, and spasticity and has already been well established for most of them.[27–29] Psychotherapy and neuropsychological treatment were reported frequently in depressive patients and in those with cognitive problems. Currently, clear treatment guidelines are missing in those patients.

Treatment patterns have significantly changed over the last decade, and treatment has become more frequent compared with the interim analysis.[10] This holds true for nearly all reported symptoms (with exception of bowel dysfunctions ($p=0.08$)) and may reflect either the emergence of new treatment options[30,31] or an increasing awareness of international and national guidelines that are available for the symptomatic treatment of MS.

When looking on symptoms over course of time, besides paresis and spasticity, "soft" symptoms such as fatigue, depression, and cognition dysfunctions are frequently reported in our cohort. Impaired mobility, pain, gait disturbances, and cognitive impairment have greatest effects on the employment status in MS patients.[32] Overall retirement rate has increased from less to 20% at interim[6] analysis to 29.4%. The high prevalence of neuropsychological or emotional symptoms at all stages and in all courses of MS shows that these symptoms may have a tremendous effects on the well-being and employment (see supplemental Table 2). Recently, it was shown that patients with an EDSS of 3–6 use more intensively cognitive or behavioral coping techniques than less or severely impaired patients,[33] which underlines the importance that neuropsychological symptoms need to be recognized and appropriately treated.

Another focus of our study was on initial symptoms in the context of MS. Dysesthesia was the most common initial symptom in our cohort. A difference was found depending on disease course. The prevalence of dysesthesias ($p<0.001$) and visual disturbances ($p<0.001$) as initial symptoms was significantly higher for RRMS patients, whereas in PPMS patients paresis ($p<0.001$) was the leading initial symptom. In addition, RRMS patients had a lower age of disease onset compared to PPMS patients (32.2 and 41.4 years, $p<0.001$). Despite significant changes of diagnostic criteria and diagnostics, our findings are comparable with key cohort studies in the literature.[15–17]

Limitations of cohort and registry studies (e.g. multiple centers, different treatment patterns, and no standardization in treatment or in assessing patients) have to be mentioned. Especially for fatigue, we are aware of the drawbacks of data from registries. There are no assessment tools that have to be used for diagnostics. We cannot differentiate between mental or motor fatigue in our patients. Fatigue may be a side effect of administered medicine or it may be a co-morbidity to depression. Fatigue can have several causes and consequently several treatment options. But registries are

supplied with data from neurologists generated in their daily work without any laboratory conditions. Thus, these data tell us more about real-world MS than randomized controlled trials with selected patient populations. In addition, we do believe that our results will be relevant for physicians in most European countries, North America, and Australia due to the high number of patients included in our analysis and as our findings regarding initial symptoms and age of onset are in line with key studies.[15–18,34] The usefulness of observational data derived from registries in the field of MS has recently been discussed.[35] Elucidation of unmet needs and monitoring of treatment patterns are important tasks of such registries, for example, the understanding of neuropsychological symptoms like fatigue has to be focused. More knowledge about it will allow improved treatments, which has to be adapted to various causes. Fatigue has great impact on the well-being and employment even at an early stage. Planning of trials or interventional studies or the implementation of guidelines might be aspirational goals. In line with large registries, our analysis provides real-world experience and evidence.

Based upon the analysis and the findings of our study, the following conclusions and recommendations can be made:

- Neuropsychological impairments are one of the most reported symptoms—even at an early stage of disease—and of the utmost importance.
- Fatigue is the most reported symptom over the course of time. Awareness and treatment of fatigue are crucial. Better understanding of the various causes for fatigue is crucial. Respective trials for treatment of fatigue should be initiated.
- Especially for symptoms with no clear evidence of pharmacologic interventions, guidelines or trials should be initiated; and the need for psychological support and physical and occupational therapy has to be established and appropriate treatment given.
- Sexual dysfunctions are underreported compared to other reports from registries. The reasons for this still have to be investigated.

Acknowledgements

Sandra Cox edited the manuscript for non-intellectual content. We would like to thank the following centers for patient recruitment and data collection: Alexianer Misericordia GmbH—Augustahospital Anholt, Klinik für Neurologie, Isselburg; Alexianer St. Joseph-Krankenhaus Berlin-Weißensee, MS-Ambulanz, Berlin; Alfried-Krupp-Krankenhaus, Klinik für Neurologie, Essen; Ammerland-Klinik GmbH, Klinik für Neurologie, Westerstede; Ärztehaus am Denkmal, Dr. med. T. Sühnel, Leipzig; Asklepios Fachklinikum Teupitz, Neurologische Klinik, Teupitz; Asklepios Klinik St. Georg Hamburg, Neurologische Abteilung, Hamburg; Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil gGmbH, Neurologische Klinik und Poliklinik, Bochum; Celenus Klinik für Neurologie Hilchenbach, Hilchenbach; Charité—Universitätsmedizin Berlin, Ambulanz für Multiple Sklerose und Neuroimmunologie, Berlin; Diakonie-Klinikum Schwäbisch Hall gGmbH, Neurologische Klinik, MS-Ambulanz, Schwäbisch Hall; DKD HELIOS Klinik Wiesbaden, Fachbereich Neurologie, Wiesbaden; Dr. Becker Kiliani-Klinik, Neurologische Abteilung, Bad Windsheim; DRK Kamillus-Klinik, Neurologische Abteilung, Asbach; Ernst-Moritz-Arndt-Universität Greifswald, Klinik und Poliklinik für Neurologie, Greifswald; Evangelisches Krankenhaus Bielefeld gGmbH, Neurologische Klinik Bethel, Bielefeld; Fachklinik Feldberg GmbH, Klinik am Haussee, Feldberger Seenlandschaft; Fachklinik für Neurologie Dietenbronn GmbH, Schwendi; Fachkrankenhaus Hubertusburg gGmbH, Klinik für Neurologie, Wermsdorf; Fachübergreifende Gemeinschaftspraxis Neurologie & Radiologie, Mosbach; Gemeinschaftskrankenhaus Herdecke, Abteilung für Neurologie, Herdecke; Gemeinschaftspraxis für Neurologie und Psychiatrie im Albertus Magnus Zentrum, Siegen; Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. A. Niederhofer, Dr. med. U. Kauermann, PD Dr. med. M. Küper, Bochum; Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. B. Uhlig, Dr. med. J. Windsheimer, Nürnberg; Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. F. Schmitz, Ladenburg; Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. H. B. Rickert, Dr. med. G. Enck, Dr. med. C. Jansen, Münster; Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. J. Springub, W. Schwarz, Westerstede; Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. S. Peschel und Kollegen, Leipzig; Gemeinschaftspraxis für Neurologie und Psychiatrie, Kandel; Gemeinschaftspraxis für Neurologie, Dr. med. E. Rehkopf, Dr. med. H. Gromoll, Osnabrück; Gemeinschaftspraxis für Neurologie, Dr. med. R. Loos, R. Hasselbach, Alzey; Gemeinschaftspraxis Nervenstark, Dr. med. A. K. Bach, Dr. med. T. Morgenbesser, Dr. med. C. Venker, Essen; Hardtwaldklinik I, Neurologisches Zentrum, Bad Zwesten; Heilig Geist-Krankenhaus, Klinik für Neurologie, Köln; HELIOS Fachkliniken Hildburghausen, Fachbereich Neurologie, Hildburghausen; Helios Klinik Hagen Ambrock, Klinik für Neurologie, Hagen; HELIOS Rehaklinik Damp GmbH, Abteilung Neurologie, Damp; Herz-Jesu-Krankenhaus Hiltrup

GmbH, Klinik für Neurologie mit Klinischer Neurophysiologie, Münster; Kath. Kliniken Emscher-Lippe GmbH, St. Barbara-Hospital, Neurologische Abteilung, Gladbeck; Klinik am Stein, Ambulantes Reha-Zentrum, Dortmund; Kliniken Schmieder Konstanz, Konstanz; Klinikum Augsburg, Neurologische Klinik, Augsburg; Klinikum Bayreuth GmbH, Klinik Hohe Warte, Klinik für Neurologie, Bayreuth; Klinikum der Johann Wolfgang Goethe-Universität, Zentrum der Neurologie und Neurochirurgie, Frankfurt/Main; Klinikum der Stadt Ludwigshafen am Rhein gGmbH, Neurologische Klinik, Ludwigshafen; Klinikum der Universität zu Köln, Klinik und Poliklinik für Neurologie, Köln; Klinikum Herford, Klinik für Neurologie, MS-Ambulanz, Herford; Klinikum Lippe-Lemgo, Neurologische Klinik, Lemgo; Klinikum Osnabrück GmbH, Neurologische Klinik, Osnabrück; Klinikum Stuttgart, Katharinenhospital, Neurologische Klinik, Neurozentrum, Stuttgart; Knappschaftskrankenhaus Recklinghausen, Klinik für Neurologie und Klinische Neurophysiologie, Recklinghausen; Knappschaftskrankenhaus Sulzbach, Neurologische Klinik, Sulzbach; Kopfzentrum Leipzig, Dr. med. E. Strauß, Leipzig; Krankenhaus der Barmherzigen Brüder, Abteilung für Neurologie und Neurophysiologie, Trier; Krankenhaus Nordwest GmbH, Neurologische Klinik, Frankfurt/Main; LWL-Klinik Lengerich, Abteilung für Neurologie, Lengerich; m&i-Fachklinik Ichenhausen, Abteilung für Neurologie, Ichenhausen; Märkische Kliniken GmbH, Klinikum Lüdenscheid, Klinik für Neurologie, Lüdenscheid; MediClin Klinikum Soltau, Neurologische Klinik, Soltau; MediClin Reha-Zentrum Bad Orb, Fachklinik für Neurologie und klinische Neuropsychologie, Bad Orb; Medizinisches Versorgungszentrum Düren—Lendersdorf, Düren; Medizinisches Versorgungszentrum für Neurologie, Psychiatrie und Psychotherapie, Dr. med. E. Mirzaian, F. Köhler, Herne; Medizinisches Versorgungszentrum Hemmoor, Zentrum für Sozialpsychiatrie und Nervenheilkunde GmbH, Hemmoor; Medizinisches Versorgungszentrum Schlüchtern GmbH, Praxis für Neurologie, Schlüchtern; MVZ für Neurologie und Psychiatrie in Bremen Nord, Bremen; MVZ Immenstadt Allgäu GmbH, Praxis für Neurologie, Immenstadt; Nervenärztliche Gemeinschaftspraxis, Dr. med. N. Katte, Dr. med. F. Vogelsang-Dietz, Dr. med. B. Graf, Lünen; Nervenärztliche Gemeinschaftspraxis, Dr. med. R. Roth, B. Schmitt-Roth, Prof. Dr. med. M. Weih, Nürnberg; Neurologicum Aachen, Neurologische Gemeinschaftspraxis, Aachen; Neurologie am Ludgeriplatz, Gemeinschaftspraxis für Neurologie und Psychiatrie, Münster; Neurologie an der Hase, Gemeinschaftspraxis für Neurologie und Psychiatrie, Osnabrück; Neurologische Facharztpraxis, Dr. med. I. Nastos, Bochum; Neurologische Gemeinschaftspraxis am Klieversberg, Dr. med. W. Hallermann, Dr. med. V. Otto, J. Hoffmann, Wolfsburg; Neurologische Gemeinschaftspraxis im medicentrum, Dr. med. V. Gillwald, Dr. med. T. Simm, Dr. med. F. Wiese, Mönchengladbach; Neurologische Gemeinschaftspraxis Kassel Vellmar, C. Lassek, Dr. med. A. Ammerbach, Dr. med. A. Fetzer, M. Fischer, Kassel; Neurologische Gemeinschaftspraxis, Dr. med. B. Haerting, Dr. med. P Debleecker, Oberhausen; Neurologische Gemeinschaftspraxis, Dr. med. K. Brandi, Dr. med. C. Pilz, Mannheim; Neurologische Gemeinschaftspraxis, Dr. med. S. Gierer, Dr. med. S. Gierer, Dillingen; Neurologische Gemeinschaftspraxis, Prof. Dr. med. S. Wagner, Dr. med. M. Kaltenmaier, Schwetzingen; Neurologische Klinik GmbH, Campus Bad Neustadt, Bad Neustadt; Neurologische Klinik Selzer GmbH, Baiersbronn-Schönmünzach; Neurologische Praxis, Dr. med. M. Bauer, Minden; Neurologische Praxis, Dr. med. M. Rösener, Stuttgart; Neurologische Praxis, Dr. med. W. K. Blersch, Regensburg; Neurologische Praxis, R. Berkenfeld, Neukirchen-Vluyn; Neurologische Praxis, U. Kullik, Eisleben; Neurologische Praxisgemeinschaft, Sprockhövel; Neurologisches Rehabilitationszentrum Godeshöhe e.V., Bonn; Neurologisches Rehabilitationszentrum Quellenhof, Bad Wildbad; Neurologisch-Psychiatrische Berufsausübungsgemeinschaft, Dr. med. M. Appy und Kollegen, Stuttgart; Neurologisch-Psychiatrische Gemeinschaftspraxis, Dr. med. J. Schierenbeck und Kollegen, Wolfenbüttel; NeuroMed Campus, Prof. Dr. med. G. Nelles und Kollegen, Köln; NeuroMVZ Stuttgart—SynConcept GmbH, Stuttgart; Neuropsychiatricum, Zentrum für Neurologie, Psychiatrie und Psychotherapie, Ludwigshafen; Neurozentrum am Klosterforst, Dr. med. K. Gehring, Itzehoe; Neurozentrum Bielefeld-Brackwede, Bielefeld; Neurozentrum Kaltenkirchen, M. Freidel, Kaltenkirchen; Neurozentrum Schlosscarree, Dr. med. E. Klippel, Dr. med. V. Moshagen, Braunschweig; Oberhavel Kliniken GmbH, Klinik Hennigsdorf, Neurologische Abteilung, Hennigsdorf; Praxis für Neurologie und Psychiatrie, Dr. med. A. Kowalik, Stuttgart; Praxis für Neurologie und Psychiatrie, Dr. med. C. Schenk, Osnabrück; Praxis für Neurologie und Psychiatrie, Dr. med. C. Tümmers, I. Humpert-Glosemeyer, Dr. med. S. Kaul, Ibbenbüren; Praxis für Neurologie und Psychiatrie, Dr. med. E. Bollensen, Eschwege; Praxis für Neurologie und Psychiatrie, Dr. med. G. Pfeffer, Dr. med. M. Staudinger-Pfeffer, Landshut; Praxis für Neurologie und Psychiatrie, Dr. med. H.-M. Schult, A. Löffler-Wulff, Hamburg; Praxis für Neurologie und Psychiatrie, Dr. med. J. Beutler, Braunschweig; Praxis für Neurologie und Psychiatrie,

Dr. med. J.-D. Seybold, Würzburg; Praxis für Neurologie und Psychiatrie, Dr. med. M. Springer, Pirmasens; Praxis für Neurologie und Psychiatrie, Dr. med. W.-E. Hofmann, Aschaffenburg; Praxis für Neurologie, Dr. med. S. Heimburger, Tirschenreuth; Praxis für Neurologie. L. Daume, Halle; Praxis rechts vom Rhein, PD Dr. med. H.-F. Petereit, Dr. med. J.-D. Seifert, Köln; Praxisgemeinschaft für Neurologie und Psychiatrie, Dr. med. W.-G. Elias, Dr. med. B. Elias-Hamp, Dr. med. C. Hebell-Siewers, Hamburg; Praxisgemeinschaft Kreuzau, M. Stankewitz, Kreuzau; Reha-Zentrum Nittenau GmbH, Fachklinik für Neurologische Rehabilitation, Nittenau; Rehazentrum Wilhelmshaven, Postakut- und Rehabilitationsklinikum für Orthopädie und Neurologie, Wilhelmshaven; Rhein-Mosel-Fachklinik, Zentrum für Psychiatrie, Psychotherapie und Neurologie, Andernach; Ruppiner Kliniken GmbH, Klinik für Neurologie, MS-Ambulanz, Neuruppin; Sächsisches Krankenhaus Arnsdorf, Multiple-Sklerose-Ambulanz, Arnsdorf; Sächsisches Krankenhaus für Psychiatrie und Neurologie, Klinik für Neurologie, Rodewisch; Segeberger Kliniken GmbH, Neurologisches Zentrum, Bad Segeberg; SRH Waldklinikum Gera gGmbH, Klinik für Neurologie, Gera; St. Josef-Hospital, Klinikum der Ruhr-Universität Bochum, Klinik für Neurologie, Bochum; St. , Klinik für Neurologie, MS-Ambulanz, Potsdam; St. Vincenz-Krankenhaus GmbH, Neurologische Klinik, Paderborn; St.-Marien-Hospital GmbH, Neurologische Klinik, Lünen; Städtisches Klinikum Braunschweig gGmbH, Neurologische Klinik, Braunschweig; Städtisches Krankenhaus Martha-Maria Halle-Dölau gGmbH, Klinik für Neurologie, Halle; Überörtliche Gemeinschaftspraxis für Neurologie und Psychiatrie, Dr. med. D. Hense, Dr. med. M. Dietz, B. Cornelius, Ibbenbüren; Universitätsklinikum Carl Gustav Carus Dresden, Multiple Sklerose Zentrum, Dresden; Universitätsklinikum des Saarlandes, Neurologische Klinik, Homburg; Universitätsklinikum Erlangen, Klinik für Neurologie, Erlangen; Universitätsklinikum Heidelberg, Neurologische Klinik, Heidelberg; Universitätsklinikum Jena, Neurologische Klinik, Jena; Universitätsklinikum Münster, Klinik für Allgemeine Neurologie, Münster; Universitätsklinikum Regensburg, Klinik und Poliklinik für Neurologie am Bezirksklinikum Regensburg, Regensburg; Universitätsklinikum Tübingen, Zentrum für Neurologie, Tübingen; Universitätsklinikum Ulm, Klinik und Poliklinik für Neurologie, Ulm; Universitätsklinikum Würzburg, Neurologische Klinik und Poliklinik, Würzburg; Universitätsmedizin Göttingen, Klinik für Neurologie, Göttingen; Universitätsmedizin Rostock, Klinik und Poliklinik für Neurologie, Rostock; Westerwaldklinik Waldbreitbach gGmbH, Rehabilitationszentrum für Neurologie und Neurologische Psychosomatik, Waldbreitbach; Wicker-Klinik, Neurologische Abteilung, Bad Wildungen; Zentrum für Neurologie, Psychiatrie und Psychotherapie, Asperg; and ZNS-Kamen, Praxisgemeinschaft für Neurologie, Psychiatrie und Psychotherapie, Kamen.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Paulus S Rommer reports compensation from Biogen Idec, Merck Serono, Roche, Sanofi Genzyme, and Shire. None resulted in a conflict of interest relevant to the content of the submitted manuscript. Kerstin Eichstädt reports no disclosure relevant to the content of the submitted manuscript. David Ellenberger reports no disclosure relevant to the content of the submitted manuscript. Peter Flachenecker reports speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, Genzyme, Novartis, Merck Serono, Roche and Teva. He has participated in pharmaceutical company–sponsored trials by Almirall, Biogen and Novartis. None resulted in a conflict of interest relevant to the content of the submitted manuscript. Tim Friede reports personal fees for consultancies (including data monitoring committees) in the past 3 years from Bayer, Boehringer Ingelheim, DaiichiSankyo, Feldmann Patent Attorneys, Galapagos, Grünenthal, Janssen, Mediconomics, Novartis, Penumbra, Pharmalog, Roche, SGS, and UCB; all outside the submitted work. None resulted in a conflict of interest relevant to the content of the submitted manuscript. Judith Haas reports compensation from Almirall, Biogen, Bayer, Hoffman La Roche, Merck, Octapharma, Teva, Allergan, and Novartis. None resulted in a conflict of interest relevant to the content of the submitted manuscript. Christoph Kleinschnitz reports personal compensations for giving lectures and attending advisory boards from Biogen, Merck Serono, Bayer, Teva, Novartis, Medday, Mylan, Genzyme, Almirall, and Roche. None resulted in a conflict of interest relevant to the content of the submitted manuscript. Dieter Pöhlau reports institutional research grants and personal honoraria as speaker from Almirall, Biogen Idec, Bayer, Genzyme, Merck Serono, Novartis, Sanofi, and TEVA. None resulted in a conflict of interest relevant to the content of the submitted manuscript. Otto Rienhoff reports no disclosure relevant to the content of the submitted manuscript. Alexander Stahmann reports no disclosure relevant to the content of the submitted manuscript. Uwe K Zettl reports speaker honorary from Almirall, Bayer Pharma AG, Novartis

Pharma AG, Teva Pharma AG, Biogen IDEC, Merck Serono GmbH, and Sanofi-Aventis GmbH. None resulted in a conflict of interest relevant to the content of the submitted manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The German MS Registry is funded by the German MS Society's Trust (German MS Trust) and by the German MS Society.

ORCID iDs

Paulus Stefan Rommer https://orcid.org/0000-0001-5209-6647
Tim Friede https://orcid.org/0000-0001-5347-7441

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DOI: 10.1177/1352458518799580
URN: urn:nbn:de:hbz:465-20220331-154719-2

Rommer, P. S., et al. (2019). Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. Multiple Sclerosis Journal, 25(12), 1641–1652. https://doi.org/10.1177/1352458518799580

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