

ORIGINAL ARTICLE

The presence and burden of cognitive issues: discordance between the perception of neurologists and people living with multiple sclerosis

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Abstract

Background and purpose: Cognitive impairment is a common symptom of multiple sclerosis (MS) and occurs in more than 40% of people living with MS (plwMS). No real-world study has assessed the perception of neurologists and plwMS on cognitive issues.

Methods: Using data from the 2011–2019 Adelphi MS Disease Specific Programme database, this real-world, retrospective, cross-sectional multi-cohort study included people aged ≥ 18 years with relapsing–remitting MS and secondary progressive MS from the United States, UK and the EU. Neurologists provided data on the patient record form for plwMS, with the same plwMS invited to voluntarily complete a patient self-completion form: a questionnaire about their experiences with MS.

Results: Of 25,374 plwMS, 4817 who provided information on cognitive and mood symptoms were included in the analysis. Of the plwMS, 68% and 59% reported feeling ‘mentally fatigued’ and having ‘difficulty concentrating’, respectively. Neurologists reported only 27% of plwMS as having ‘difficulty concentrating’ and 15% of plwMS as having ‘short-/long-term memory problems’. Neurologists reported cognitive or mood symptoms as ‘not experienced’ by a higher percentage of participants with relapsing–remitting MS than secondary progressive MS. Of the plwMS who experienced ‘difficulty concentrating’, most had a concomitant feeling of being ‘mentally fatigued’ (52%), followed by ‘feeling anxious or tense’ (49%) and ‘feeling depressed’ (44%). In plwMS, caregivers reported ‘difficulty concentrating’ (16%) as the most common cognitive issue.

Conclusion: A clear discordance was observed between neurologists and plwMS regarding the perception of the cognitive and neuropsychiatric issues. These results underline the under-perception of cognitive and emotional affective symptoms in plwMS during neurological consultations.

KEYWORDS

cognitive issues, multiple sclerosis, neurologists, perception, plwMS

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INTRODUCTION

Multiple sclerosis (MS) is a neurological disease with an estimated global prevalence, in 2020, of 35.9 (95% confidence interval 35.87; 35.95) per 100,000 people [1]. Cognitive impairment (CI), a common symptom of MS, occurs in 41%–70% of people living with MS (plwMS) across all subtypes and at all stages of the disease [2–5]. It can affect different cognitive domains, including working memory, information processing speed, concentration and executive functions [6, 7]. The presence of CI in the early stages of MS may be predictive of disease progression in the long term; its prevalence increases with disease progression and it is more prevalent in the progressive forms of MS [8]. A long-term study showed an increase in the presence of cognitive dysfunction from 25% to 56% in people with early-onset MS over a 10-year period [9]. Cognitive dysfunction affects several aspects of the lives of plwMS, including daily activities, employment status, participation in social activities, driving ability, quality of life (QoL), psychosocial functions and disease management [6, 10, 11].

Although efforts are constantly being made to improve the diagnosis of CI and the importance of routine assessment of cognitive status is emphasized in recommendations from the United States National MS Society [12] and the German Neurological Society [13], many neurologists still skip the routine assessment of cognitive status during consultations, attributing this to a lack of time, resources and experience and reimbursement [12, 14]. Thus, CI largely remains undiagnosed in plwMS.

Several recent studies show a discordance between plwMS and neurologists on the perception of symptoms that plwMS feel impact their QoL [15–17]. Neurologists tend to focus on the impact of MS on physical disability progression, relapses and disease activity, but may not consider its impact on mental and social wellbeing [17]. In a multicentre study including 171 patients with relapsing–remitting multiple sclerosis (RRMS), Heesen et al. evaluated differences between patients and physicians in their perception of 13 bodily functions. By analysing first choices, visual function was followed by cognition (thinking and memory), walking ability and lack of pain by most of the patients. Physicians, on the other hand, stressed walking ability much higher followed by cognition and wakefulness/alertness. In contrast to patients, visual function gained only low priority [18].

Increasingly the therapeutic relationship between the physician and the person being treated is moving towards a shared decision model. This is also true for the management of MS, with the goal being that the neurologist and plwMS will discuss and address both the physical aspects of the disease and the major QoL concerns [19].

Issues leading to reduced QoL for plwMS can also affect their caregivers who have reported suffering from distress and reduced QoL as well [20]. Psychiatric symptoms and CI in plwMS are the major contributors to caregiver distress [20].

No real-world study has yet explored the discordance between neurologists and plwMS on the perception of cognitive and

neuropsychiatric issues. Therefore, the present study analysed the similarities and differences in reported perspectives of plwMS when dealing with MS (both RRMS and secondary progressive MS [SPMS]), their caregivers and their neurologists using the Adelphi MS Disease Specific Programme (DSP) database. The study also explored the coexistence of cognitive issues, mental fatigue and depression in plwMS. Finally, the study assessed the burden on caregivers of caring for plwMS in terms of the most troublesome activities and symptoms.

METHODS

Study design and population

This was a retrospective–prospective, descriptive, non-interventional, cross-sectional, multi-cohort study of patients clinically diagnosed with MS (RRMS and SPMS) using a secondary source of data, the Adelphi MS DSP database. This database is part of a disease-specific multinational ongoing study that captures real-world clinical practice and perceptions of plwMS, caregivers and neurologists. The real-world study investigated a cohort of people living with RRMS or people living with SPMS from the United States, UK or the EU (France, Germany, Italy and Spain) using data from 1 January 2011 until 31 December 2019 of the Adelphi MS DSP database (waves I–VIII). All plwMS were identified through neurologists or MS nurses. Participation in the study was entirely voluntary and consent was obtained from patients and caregivers.

Inclusion and exclusion criteria

People with a clinical diagnosis of RRMS or SPMS and an age ≥ 18 years were included. PlwMS with an unknown age or who were < 18 years old and those with a diagnosis of primary progressive MS were excluded.

End-points

The primary end-point was the proportion and number of plwMS who self-reported cognitive or mood symptoms, worries about their condition and the effects of cognitive problems in the workplace. The secondary end-points were the proportion and number of

- plwMS reported to have cognitive or mood symptoms;
- plwMS with cognitive symptoms as reported by plwMS versus their neurologists;
- plwMS who reported both cognitive and mood symptoms or reported cognitive or mood symptoms in isolation;

- caregivers of plwMS who reported cognitive or mood symptoms and the cognitive activities that require support on a daily basis by plwMS;
- caregivers of plwMS who reported cognitive and mood symptoms as the most troublesome activities when looking after plwMS.

Data collection

The neurologists who participated in the study were asked to provide data on a patient report form (PRF) for the next 10 plwMS to have a consultation; the same plwMS were invited to complete a patient self-completion form (PSC) providing their own evaluation of their symptoms. Caregivers of plwMS were asked to fill out a caregiver self-completion form. The burden of cognitive issues was measured by asking the question to both patients and neurologists on 'difficulty concentrating'. However, the other questions asked differed between plwMS and neurologists. PlwMS were asked questions about 'worries related to MS', 'fatigue' and 'depression' and whether they 'felt anxious or tense'. Neurologists were asked about 'short-/long-term memory problems', 'nominal asphasia' and 'low mood/depression' in their patients. Brief descriptions of the primary and secondary objectives and the survey forms used for each objective are provided in [Table 1](#). The survey forms are the intellectual property of Adelphi Real World and can be made available subject to approval by Adelphi.

Statistical analysis

This study was based on detailed PRFs completed by neurologists and self-completed questionnaires by plwMS and caregivers. From the start of the study, the clinical data were collected annually from neurologists. The data were analysed for the plwMS for whom both a PRF and a PSC was available. All planned analyses for the primary

and secondary outcomes were descriptive except for the analysis of concordance between the burden reported by neurologists and plwMS, which was performed using Cohen's kappa statistics. For descriptive analyses, continuous variables were summarized using mean, standard deviation (SD), range, median and interquartile range (25% and 75%); categorical variables were summarized using frequency counts and percentages. Missing data were considered a separate category in all analyses and were described using frequency counts and percentages.

RESULTS

Baseline and demographic characteristics of plwMS

During the study period, neurologists provided data for 25,374 plwMS (RRMS or SPMS). Of these, 4817 plwMS provided information on cognitive and mood symptoms and were included in the analysis. The majority of plwMS were female (67%) with a mean (SD) age of 40 (11.8) years. The mean (SD) time since diagnosis was 5.85 (6.195) years for the plwMS. The mean (SD) most recent Expanded Disability Status Scale score was 2.3 (1.8).

For plwMS who answered the type of work question ($n=3097$), 50% were working full time and 76% had professional or skilled work. Demographics and other baseline characteristics are presented in [Table 2](#).

Impact of cognitive issues, including in the workplace, reported by plwMS

Of the total plwMS ($N=4817$), 3276 (68%) reported 'feeling mentally fatigued' and 2864 (59%) reported having 'difficulty concentrating'. A higher proportion of participants with SPMS than RRMS reported cognitive and mood symptoms ([Figure 1a](#)). When classified by

TABLE 1 Objectives and the survey form(s) used to acquire data for each objective.

Objectives	Description	Survey form(s) used
Primary	PlwMS-reported impact of cognitive issues, including in the workplace	PSC
Secondary 1	Neurologist-reported impact of cognitive issues on plwMS	PRF
Secondary 2	Comparison of plwMS and neurologist perspectives of cognitive issues	PRF and PSC
Secondary 3	PlwMS-reported impact of combined mood and cognitive issues	PSC
Secondary 4	Caregiver-reported cognitive issues and cognitive activities for the plwMS that require help	CSC
Secondary 5	Caregiver-reported most troublesome cognitive issues and activities of the plwMS	CSC

Abbreviations: CSC, caregiver self-completion form; plwMS, people living with multiple sclerosis; PRF, patient record form; PSC, patient self-completion form.

TABLE 2 Demographics and other baseline characteristics of plwMS.

Characteristic	Total patients (RRMS, SPMS)	RRMS	SPMS
Baseline (N)	4817	4320	497
Age (years), mean (SD)	40 (11.8)	38.9 (11.5)	49.4 (9.5)
Age category			
≥18–30	1214 (25)	1201 (28)	13 (3)
31–40	1463 (30)	1381 (32)	82 (16)
41–50	1136 (24)	980 (23)	156 (31)
51–60	735 (15)	547 (13)	188 (38)
61–70	244 (5)	192 (4)	52 (10)
71–80	24 (0)	19 (0)	5 (1)
>80	1 (0)	0	1 (0)
Sex			
Male	1591 (33)	1412 (33)	179 (36)
Female	3226 (67)	2908 (67)	318 (64)
Baseline (N)	3852	3517	335
Time since diagnosis (days), mean (SD)	5.85 (6.19)	5.23 (5.68)	12.36 (7.54)
Baseline (N)	4817	4320	497
Employment status			
Working full time	2385 (50)	2281 (53)	104 (21)
Working part time	687 (14)	612 (14)	75 (15)
On long-term sick leave	79 (2)	58 (1)	21 (4)
Homemaker	500 (10)	415 (10)	85 (17)
Student	354 (7)	353 (8)	1 (0)
Retired	369 (8)	255 (6)	114 (23)
Unemployed	383 (8)	293 (7)	90 (18)
Don't know	60 (1)	53 (1)	7 (1)
Baseline (N)	3097	2911	186
Type of work			
Professional or skilled work	2360 (76)	2205 (76)	155 (83)
Manual work	573 (19)	548 (19)	25 (13)
Don't know	164 (5)	158 (5)	6 (3)
Baseline (N)	4817	4320	497
Home circumstances			
Lives alone	767 (16)	708 (16)	59 (12)
Lives with partner/spouse	3301 (69)	2931 (68)	370 (74)
Lives with other family/friends	728 (15)	670 (16)	58 (12)
Nursing home	13 (0)	6 (0)	7 (1)
Sheltered housing	6 (0)	3 (0)	3 (1)
Day care/respite care	2 (0)	2 (0)	0
Homeless	0	0	0
Baseline (N)	3933	3606	327
Number of relapses in the last 12 months			
0	2318 (59)	2088 (58)	230 (70)
1	1113 (28)	1044 (29)	69 (21)
2	393 (10)	373 (10)	20 (6)
3	63 (2)	59 (2)	4 (1)
≥4	46 (1)	42 (1)	4 (1)

TABLE 2 (Continued)

Characteristic	Total patients (RRMS, SPMS)	RRMS	SPMS
Baseline (N)	4136	3707	429
Most recent EDSS score, mean (SD)	2.3 (1.8)	2 (1.6)	4.7 (1.7)
Baseline (N)	2257	1913	344
EDSS score at the start of the current diagnosis, mean (SD)	2.1 (1.4)	1.8 (1.2)	3.7 (1.5)
Baseline (N)	3604	3193	411
EDSS score 12 months ago, mean (SD)	2.4 (1.7)	2.1 (1.5)	4.5 (1.7)

Note: Data are presented as *n* (%) unless stated otherwise.

Abbreviations: EDSS, Expanded Disability Status Scale; N, total number of plwMS; plwMS, people living with multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

severity, a higher proportion of participants with SPMS compared to RRMS reported 'moderate' or 'extreme' cognitive and mood symptoms (Figure 1b).

Overall, in plwMS, changes in their MS led to reduced weekly working hours (12%), changes to their current job (8%) or having to stop working (8%). Furthermore, changes due to MS were more common in participants with SPMS than RRMS, including reduced weekly working hours (19% vs. 11%), early retirement (20% vs. 5%), inability to get a job (9% vs. 3%) and having to stop working (24% vs. 6%) (Table S1). In 21% of plwMS, the most common levels at which MS affected productivity during work hours were level 1 ($n=600/2796$) and level 2 ($n=5846/2796$) on a Likert scale from 0 (no effect on work) to 10 (prevents work). On comparing by the type of MS, the effect was more pronounced in participants with SPMS compared to RRMS (level 4; 46/178 [26%] vs. 266/2618 [10%]) (Table S1).

Impact of cognitive issues on plwMS, reported by neurologists

Of the total plwMS, neurologists reported 1252/4304 (29%) as having 'low mood/depression', 1164/4328 (27%) as having 'difficulty concentrating' and 632/4195 (15%) as having 'short-/long-term memory problems'. Neurologists reported a higher proportion of participants with SPMS than RRMS as having cognitive and mood symptoms (Figure 2a). When classified by severity, neurologists reported cognitive or mood symptoms as 'not experienced' by a higher percentage of participants with RRMS than SPMS. For those reported to have cognitive or mood symptoms, neurologists reported them to be 'mild' or 'moderate' in a higher proportion of participants with SPMS than RRMS (Figure 2b).

Comparison of plwMS and neurologist perspectives of cognitive issues

'Difficulty concentrating' as perceived by plwMS and neurologists

A total of 2643/4294 (62%) plwMS reported 'difficulty concentrating' in the past 2 weeks. For the same participants, neurologists

reported 1158/4294 (27%) as currently having 'difficulty concentrating'. Thus, there was a meaning discordance in the perception of the presence of 'difficulty concentrating' between neurologists and plwMS ($\kappa=0.1622$).

When assessed by the type of MS, the discordance was larger between plwMS and neurologists for participants with RRMS compared to SPMS. A total of 2266/3850 (59%) participants with RRMS reported 'difficulty concentrating' in the past 2 weeks. For the same participants, neurologists reported 954 (25%) as currently having 'difficulty concentrating' ($\kappa=0.1652$). In participants with SPMS, 377/444 (85%) reported 'difficulty concentrating' in the past 2 weeks; however, neurologists reported 204 (46%) of the same group of participants as currently having 'difficulty concentrating' ($\kappa=0.0661$). The proportions of neurologists and plwMS who reported 'difficulty concentrating' classified by severity are presented in Figure 3a.

'Difficulty concentrating' as perceived by plwMS and 'short-/long-term memory problems' in the same set of plwMS as reported by neurologists

Overall, 2553/4163 (61%) participants with SPMS reported 'difficulty concentrating' in the past 2 weeks. For the same participants, neurologists reported 628/4163 (15%) as currently having 'short-/long-term memory problems'. A stronger discordance in the perception of the presence of 'difficulty concentrating' and 'short-/long-term memory problems' between plwMS and neurologists was observed ($\kappa=0.0725$).

When assessed by the type of MS, the discordance between plwMS and neurologists was larger in participants with RRMS than SPMS. Of the participants with RRMS, 2184/3725 (59%) reported 'difficulty concentrating' in the past 2 weeks. In the same group, neurologists reported 478 (13%) as currently having 'short-/long-term memory problems' ($\kappa=0.0723$). Further, 369/438 (84%) participants with SPMS reported 'difficulty concentrating' in the past 2 weeks. For the same participants, neurologists reported 150 (34%) as currently having 'difficulty concentrating' ($\kappa=-0.0013$). The proportions of plwMS who reported 'difficulty concentrating' and neurologists who reported 'short-/long-term memory problems', classified by severity, are presented in Figure 3b.

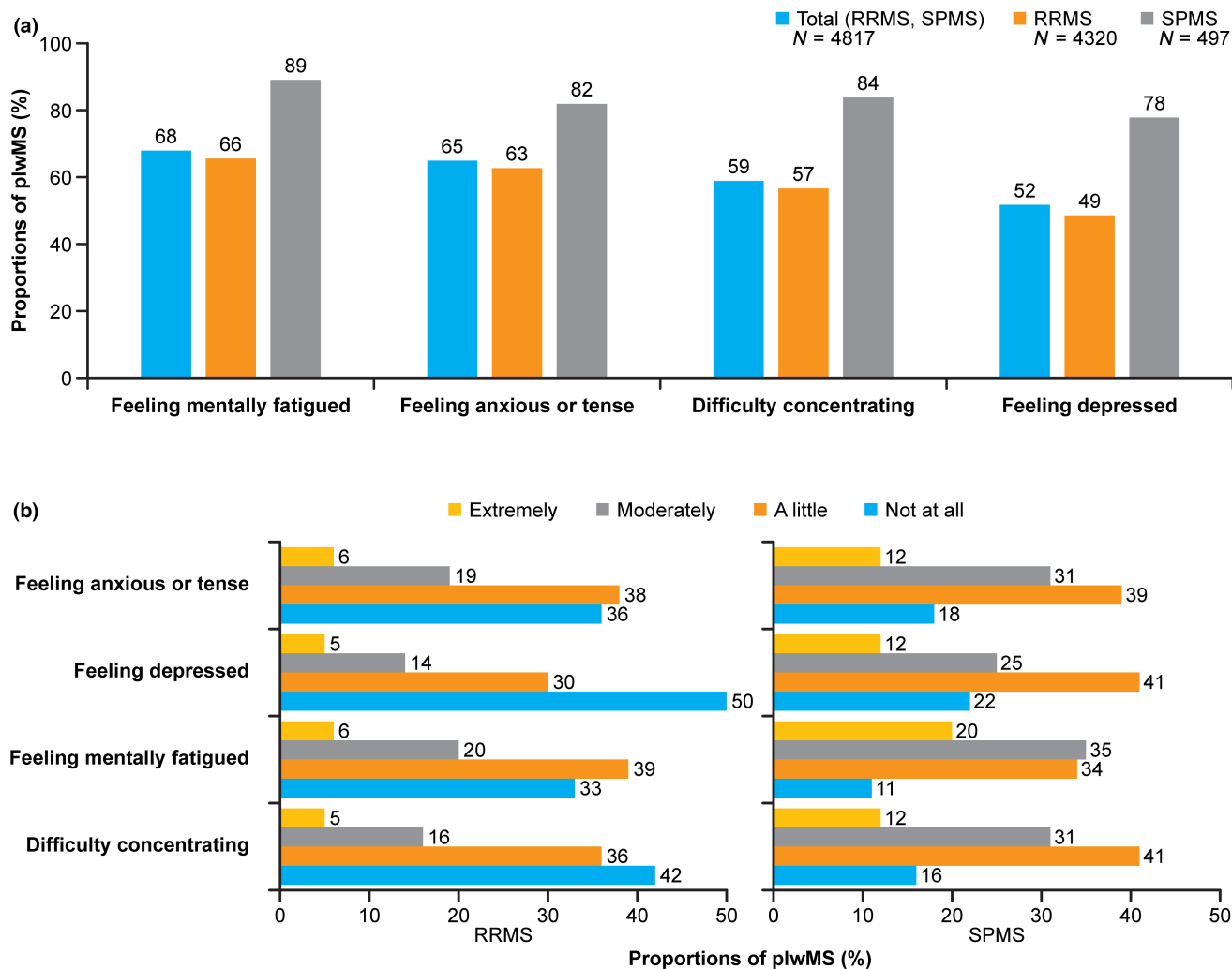


FIGURE 1 (a) Cognitive and mood symptoms and (b) their classification by severity reported by plwMS. Approximately 1% of plwMS did not state the impact of symptoms. However, the percentages are calculated from the total number of plwMS who filled the PSC form, i.e. for total RRMS or SPMS, $N=4817$, RRMS, $N=4320$, and SPMS, $N=497$. plwMS, people living with multiple sclerosis; PSC, patient self-completion form; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Impact of combined mood and cognitive issues reported by plwMS

Of the plwMS who experienced ‘difficulty concentrating’, most had concomitant feelings of ‘mental fatigue’ (2526/4775, 53%), followed by ‘feeling anxious or tense’ (2371/4775, 50%) and ‘feeling depressed’ (2116/4775, 44%) (Figure 4a). In participants with RRMS who experienced ‘difficulty concentrating’, the highest proportion had concomitant feelings of being ‘mentally fatigued’ (2131/4280, 50%), followed by ‘feeling anxious or tense’ (2036/4280, 48%) and ‘feeling depressed’ (1758/4280, 41%). In participants with SPMS who experienced ‘difficulty concentrating’, concomitant feelings of being ‘mentally fatigued’ was the most common (395/495, 80%), followed by ‘feeling anxious or tense’ (365/495, 74%) and ‘feeling depressed’ (358/495, 72%).

Of the plwMS who experienced ‘mental fatigue’, the highest proportion had a concomitant feeling of being ‘anxious or tense’

(2560/4774, 54%), followed by ‘feeling depressed’ (2188, 49%) (Figure 4b). In participants with RRMS who experienced ‘mental fatigue’, the highest proportion had a concomitant feeling of being ‘anxious or tense’ (2178/4280, 51%), followed by ‘feeling depressed’ (1821, 43%). In participants with SPMS ($N=497$) who experienced ‘mental fatigue’, the concomitant feeling of being ‘anxious or tense’ (382/494, 77%) was the most common followed by ‘feeling depressed’ (367/494, 74%).

Caregiver-reported cognitive issues and the most troublesome symptoms in plwMS for caregivers

Caregivers reported that in plwMS ($N=1689$) ‘difficulty concentrating’ (16%) was the most common symptom of CI, followed by memory loss (9%) and problems learning new tasks (7%) (Table S2). The most common troublesome symptoms for caregivers ($N=1296$)

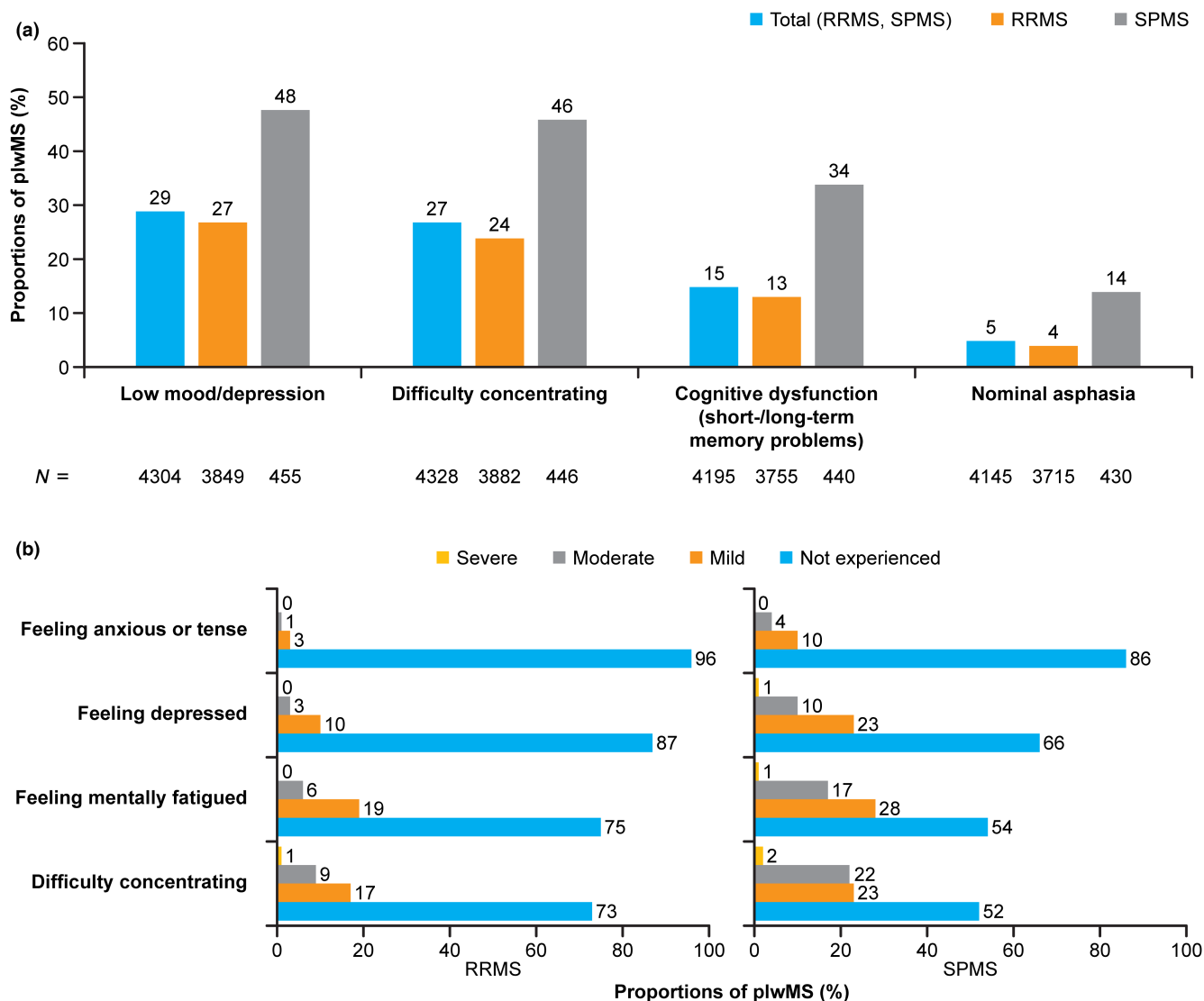


FIGURE 2 (a) Cognitive and mood symptoms and (b) their classification by severity in plwMS as reported by neurologists. plwMS, people living with multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

whilst taking care of plwMS were walking or mobility problems (24%), fatigue (21%) and weakness in muscles (17%). Similar findings were observed when assessed by the type of MS (Table S3).

Caregiver-reported activities of plwMS that require daily assistance

Overall, the most common activities of plwMS (N=1296) requiring daily assistance by caregivers were providing emotional support/encouragement (75%), helping with shopping (44%) and driving them to work/a hospital/an appointment (43%). Caregivers (N=595) reported providing emotional support/encouragement as the most troublesome activity that required daily assistance (35%). The findings were similar findings when assessed by the type of MS (Table S4).

DISCUSSION

This study explored the burden of cognitive issues in plwMS from the perspectives of neurologists, plwMS and caregivers. Overall, most of the plwMS reported the presence of cognitive and mood symptoms perceived as more severe by participants with SPMS than RRMS. In addition, participants with SPMS were perceived to have a higher severity of cognitive issues by neurologists and caregivers. A large percentage of the plwMS reported the coexistence of anxiety, difficulty concentrating, depression and mental fatigue. There was also a clear discordance between neurologists and plwMS when reporting difficulty concentrating and memory problems, which could be partially attributed to the different focus in the questionnaires. These results demonstrate that neurologists underestimated the burden of cognitive issues in plwMS, suggesting them to be undiagnosed or misdiagnosed.

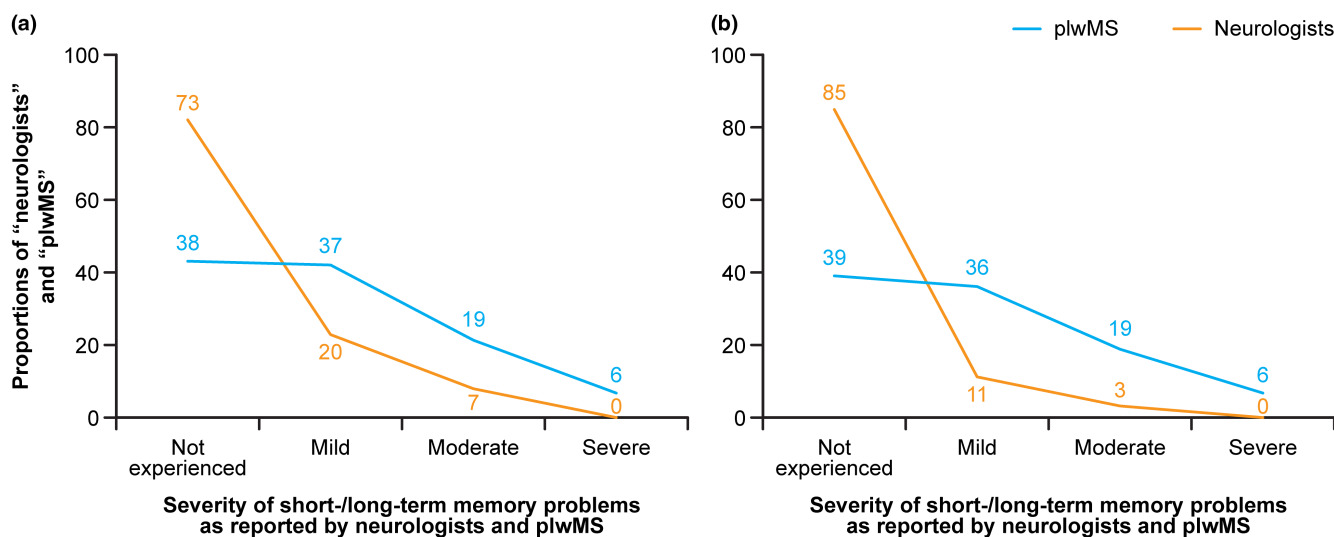


FIGURE 3 Proportion of neurologists and plwMS who reported 'difficulty concentrating' and 'short-/long-term memory problems' classified by severity. The discordance in the perception of 'difficulty concentrating' between neurologists and plwMS was calculated only for the numbers of plwMS for whom a neurologist ($N=4294$) has filled in the questionnaire. The discordance in the perception of 'short-/long-term memory problems' between neurologists and plwMS was calculated only for the numbers of plwMS for whom a neurologist ($N=4163$) has filled in the questionnaire. plwMS, people living with multiple sclerosis.

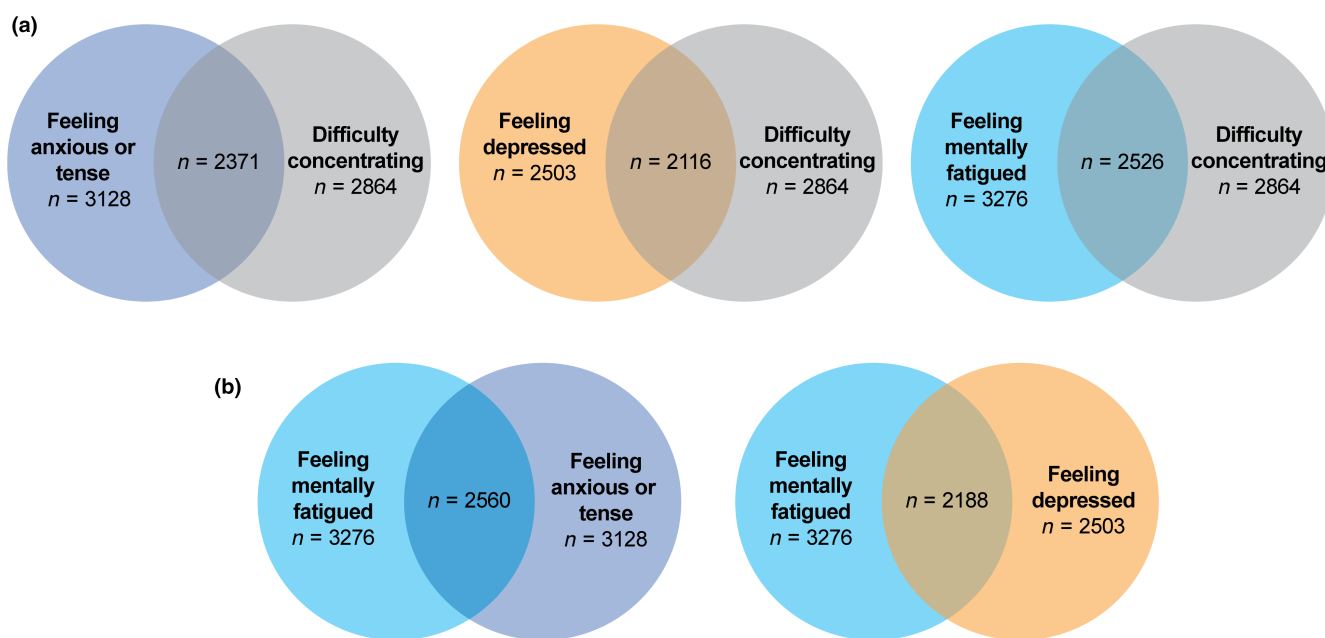


FIGURE 4 Coexistence of plwMS-reported symptoms of mood issues and (a) difficulty concentrating or (b) mental fatigue. plwMS, people living with multiple sclerosis.

Comparable results were observed in a prior cross-sectional study where plwMS considered cognitive and memory problems, fatigue and pain important whilst neurologists considered physical aspects such as imbalance, falls, ambulation issues and urinary incontinence to be the important issues [17]. Another study showed that 63% of patients, in contrast to only 11% of neurologists, considered mental health to be a relevant QoL domain [21].

Cognitive issues coexist with mood issues such as depression, anxiety and fatigue. The results of the study assessing the impact

of depression, fatigue and disability on cognitive functions showed that the existence of one or both of depression and fatigue symptoms significantly affects cognitive function [22]. Depression and anxiety are reported to impact processing speed, memory and executive functioning in plwMS [23]. In previous studies, measures of depression have been reported to correlate ($r=0.42$, $p<0.01$) with self-reported cognitive functioning as measured by the MSNQ [24, 25]. The correlation coefficients were comparable to our study where approximately 40%–50% of plwMS reported coexistence

of mood symptoms and cognitive issues. The strength of the correlation, however, decreases when cognition is tested objectively ($r = -0.17$; $p = 0.0001$) [26], emphasizing that self-reported cognitive abilities are not always accurate, particularly if the patient is experiencing depression or fatigue [27]. Furthermore, treatment of depression and fatigue symptoms can influence patients' abilities to accurately perceive their cognitive performance [27]. Strober and colleagues investigated the association of self-reported cognitive concerns on the perceived deficits questionnaire with objective cognitive measures as well as depression, anxiety, fatigue and self-efficacy in 70 plwMS [28]. They found that subjective cognitive concerns were correlated with only one objective measure of simple attention. However, no association was observed between objective performance on the remaining tests of memory, processing speed, working memory or executive functioning and subjective cognitive concerns on the perceived deficits questionnaire. In a multinational, cross-sectional, observational study of patients with MS ($N = 16,808$) conducted in 16 European countries, usual activities, pain/discomfort and anxiety/depression were moderately correlated with fatigue, and usual activities and anxiety/depression were moderately correlated with cognition [29]. Furthermore, a potential role of depression as mediator between fatigue and mental QoL was observed in plwMS in an analysis of cross-sectional data from an international cohort of 2104 plwMS [30].

In a cross-sectional, observational study, the broader category of symptoms such as current fatigue and CI were reported by 95% and 71% respectively of plwMS [31]. However, in the present study, plwMS were asked questions focusing on specific cognitive issues, and rate their issues as not experienced, mild, moderate or severe. Thus, in contrast to the European study that captured the broadest category of CI, this study captured specific issues such as feeling anxious or tense and difficulty concentrating.

Cognitive dysfunction leads to reduced productivity and is a more common cause of job loss than a physical disability [31]. CI is associated with difficulties in getting a job and/or reduced work hours [32]. This is supported by the present study where plwMS reported that cognitive issues led to reduced weekly working hours, early retirement, an inability to get a job and having to stop working. The effects were more pronounced in participants with SPMS than RRMS.

Caregivers are an important part of the lives of plwMS; physical disability and cognitive dysfunction increase the support that plwMS need in activities of daily living. Several studies have assessed the burden on caregivers and reported the impact in terms of their QoL and finances [33, 34]. The present study provides insights on the burden on caregivers in terms of the activities requiring their daily assistance and the most troublesome activities for the caregivers whilst providing this daily assistance. It is therefore evident that the presence of CI in plwMS impacts the caregiver and not the plwMS alone. A holistic approach to address CI in plwMS may reduce the caregiver burden [35].

Health-related QoL is an important aspect in the treatment and management of plwMS and needs to be assessed during

consultations alongside other assessments by neurologists [36]. The findings of the present study showed that cognitive and mood symptoms were reported as more severe in participants with SPMS than in RRMS, and these findings were supported by the perspectives of the neurologists and plwMS. This highlights the need to include the perspectives of plwMS from the initial stages of the disease (i.e., from RRMS).

Several studies are being conducted to assess the use of rehabilitation therapies such as self-generated learning, a spaced learning strategy and the modified Story Memory Technique; so far these have shown positive outcomes [37–39]. Further, new treatment strategies that are oriented to behaviour, such as neuroeducation and mindfulness-based meditation targeting self-efficacy and coping mechanisms, have recently shown their positive impact on brain health in MS by improving cognitive aspects, mental fatigue, coping abilities and stress [40]. Identifying CI early in the disease course would help neurologists to plan treatment and advise patients on other cognitive rehabilitation therapies that are required to provide a better QoL for plwMS.

Although regular cognitive evaluation in plwMS has been recommended by experts for a decade, it is still not being performed by all neurologists [12]. Several obstacles hinder the inclusion of cognitive assessments during regular checkups. First, neurologists, plwMS and/or their families may have a lack of knowledge on the impact of CI in MS, the impact of some medications on cognition (such as anticholinergic medications that reduce information processing speed and memory functions) and the availability of screening and assessment tools. Other barriers to regular cognitive evaluations in clinics by neurologists include a shortage of time and resources during the consultation, a lack of referral options, the scarcity of specialized professionals, lack of knowledge on adaptation of tests and doubts about their use in defining therapeutic efficiency [41].

Also, plwMS may themselves be reluctant to undergo a cognitive evaluation due to a fear of losing their employment, licence to drive and/or custody of children. The cost of screening tools and the lack of reimbursement for screening and treatment may also add to the barriers [12, 41]. The key recommendation from the National Multiple Sclerosis Society on addressing these barriers is raising awareness and/or education for both plwMS and neurologists on the impact and management of cognitive symptoms. It also recommends performing a baseline screening with the Symbol Digit Modalities Test or other screening tool in stable patients and annual reassessment [12]. The steps need to be taken at a country, or service and hospital level to implement the recommendations to include cognitive assessments in routine MS care; this could be driven by the MS community.

LIMITATIONS

The observational nature of the study posed some limitations. First, the diagnosis of SPMS is not well established and varies across

different countries. Secondly, the data and medications recorded, particularly previous medications, might be inaccurate or subject to human/technical error. Thirdly, there may also be unexpected issues relating to missing data. As different variables and objectives rely on different survey forms, all of these could not be uniformly collected; variables and objectives may have also differed based on the disease phenotype. Lastly, cross-sectional analyses presented here generate hypotheses, in that they allow the identification of associations rather than causal relationships between variable factors and the outcomes of interest.

Additionally, the data were derived using a survey-based methodology with neurologists providing the data available at the time of the consultation. This pragmatic approach to collect the patient sample may have excluded relevant types of patients, including those not currently receiving treatment or requiring consultations with a neurologist.

Further, this study focused on questions related to difficulty concentrating, which could have led to underestimations of cognitive issues from the plwMS because the PRF did not include memory or other cognitive-related issues. Also, the question on difficulty concentrating was slightly different for neurologists and plwMS. The difference in words might indeed explain the differences observed.

CONCLUSIONS

A considerable proportion of plwMS reported cognitive and mood symptoms; participants with SPMS reported these symptoms with a higher frequency and severity than those with RRMS. Importantly, however, these symptoms were already reported to be present in a proportion of participants with RRMS, indicating that there may be an advantage in addressing cognition by the neurologists from the earliest stages of MS. A clear discordance was observed between neurologists and plwMS when reporting their perception of the presence and severity of cognitive issues; neurologists tended to under-report the existence of cognitive issues. In addition, caregivers reported difficulty concentrating as the most troublesome symptom to deal with for plwMS. Thus, under-reporting of cognitive issues might be responsible for cognition not being discussed at the time of a consultation and clearly indicates an unmet need for both plwMS and caregivers. The study highlights the need both to discuss cognition during consultations and to bring objective assessments to bear much more frequently in routine practice.

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CONFLICT OF INTEREST STATEMENT

Iris-Katharina Penner has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer Pharma, Biogen, BMS, Celgene, Sanofi-Genzyme, Janssen, Merck Serono GmbH (an affiliate of Merck KGaA), Novartis, Roche and Teva. She has received research support from the German MS Society, Celgene, Roche, Teva and Novartis. Eddie Jones is an employee of Adelphi Real World. His organization has received a subscription fee from Novartis to access some of the data used in this study. Virginia De Las Heras, Sourav Biswas, Patricia Dominguez Castro are employees of Novartis. Suzannah Hetherington, Rahul Chetlangia, Himanshu Karu and Carol Lines are former employees of Novartis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ROLE OF THE SPONSOR

Novartis employees contributed to the study design, analysis and interpretation of the data, the writing of the study report and the decision to publish the results.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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