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ORIGINAL RESEARCH

# Results from Patient Interviews on Fatigue in Progressive Multiple Sclerosis and Evaluation of Fatigue Patient-Reported Outcome (PRO) Instruments

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## ABSTRACT

***Introduction***: Fatigue is one of the most common and debilitating symptoms of multiple sclerosis (MS) but is challenging to assess and has not been comprehensively characterized in patients with progressive MS. This study aimed to (1) obtain qualitative evidence from patients with progressive MS to characterize MS-related fatigue concepts and their impacts on health-related quality of life (HRQoL), and (2) evaluate the conceptual frameworks of existing MS-specific fatigue patient-reported outcome (PRO) instruments using study data to determine the most suitable PRO instrument in this population.

***Methods***: Qualitative interviews were conducted with 30 US participants with confirmed progressive MS and fatigue in the last 6 months to assess their MS-related fatigue. Data were compared with concepts in existing PRO instruments to evaluate their relevance in progressive MS.

***Results***: Physical and mental concepts of fatigue were identified and characterized distinctly from patients with progressive MS. Most patients characterized fatigue as occurring daily and lasting several hours, with negative impacts on HRQoL. Concept mapping to existing MS-specific fatigue PRO instruments supported the Fatigue Severity Impact Questionnaire—Relapsing Multiple Sclerosis (FSIQ-RMS) as the most suitable existing option for assessing fatigue in patients with progressive MS, as it separates physical and mental aspects of fatigue and includes every highly endorsed concept reported by the interviewed patients.

***Conclusions***: This qualitative study identified meaningful physical and mental fatigue concepts in patients with progressive MS and preliminarily supports the use of the FSIQ-RMS for this population. More research is needed to fully validate this instrument for progressive MS.

**Keywords:** Fatigue; Progressive multiple sclerosis (progressive MS); Qualitative patient interview study; Patient-reported outcome (PRO); Fatigue Severity Impact Questionnaire—Relapsing Multiple Sclerosis

Kayla Scippa and Jason C. Cole are employee of ZS Associates at the time of the study.

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(FSIQ-RMS); Primary and secondary progressive multiple sclerosis (PPMS and SPMS)

**Key Summary Points**

Fatigue is one of the most common and debilitating symptoms of multiple sclerosis (MS) but is challenging to assess and has not been comprehensively characterized in patients with progressive MS.

In this study, patients with progressive MS (primary and secondary progressive MS, PPMS and SPMS) identified key concepts of both physical and mental fatigue and characterized them differently; most participants reported daily fatigue lasting several hours a day and impacting their health-related quality of life.

Based on these findings, the Fatigue Severity Impact Questionnaire—Relapsing Multiple Sclerosis (FSIQ-RMS) is potentially suitable for assessing MS-related fatigue in progressive MS (PPMS and SPMS); however, additional research is needed to validate the FSIQ-RMS in this population.

In the future, patient-reported outcome instruments that assess fatigue in progressive MS should separate physical and mental aspects of fatigue and include key concepts reported in this study.

## INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, which leads to focal lesions in the brain and spinal cord and neurodegeneration of the entire brain [1]. Clinical courses of MS are broadly characterized as relapsing–remitting (RRMS) or progressive MS, with additional modifiers being used to describe the status of ongoing disease activity (i.e., active or non-active) and progression (i.e., with or without) [2, 3]. RRMS represents approximately 58% of the MS population [4] and is characterized by acute neurological symptom flare-ups followed by stable periods of full or partial recovery. Secondary progressive MS (SPMS) is an eventual course for the majority of RRMS cases [5], whereas in primary progressive MS (PPMS), there is disability progression from disease onset. Across the spectrum of progressive MS, patients experience steady accumulation of neurological impairments and disability.

Fatigue is one of the most common and debilitating symptoms of MS, occurring in approximately 80% of the progressive MS and 60% of the non-progressive MS population, with far-reaching effects on daily activities, ability to work and health-related quality of life (HRQoL) [6, 7]. Given its profound impacts, an essential goal for patients with MS is the effective management and treatment of fatigue. However, assessing concepts of fatigue in MS is challenging because signs and symptoms of fatigue are complex and multifactorial, there is no consensus for a definition of fatigue, and the pathophysiology of fatigue is not well understood [8, 9]. Indeed, it can be difficult to differentiate concepts that arise as a direct consequence of MS pathology versus fatigue-inducing comorbidities related to MS, such as poor sleep, depression or sedating side effects from symptom management medications, or even demographic variables, such as age and activity level. These challenges underscore the criticality of validated, comprehensive assessment tools for effective management and treatment of MS-related fatigue.

Currently, multiple MS-specific patient-reported outcome (PRO) instruments are used to assess fatigue in MS clinical trials and practice, with no consensus as to the best one to use [10, 11]. We conducted a literature search of existing fatigue PRO instruments in use in the MS setting, which revealed considerable variability across PRO instrument conceptual frameworks, as well as shortcomings in terms of current standards for PRO instrument development and validation. Almost all existing MS-specific PRO instruments were developed prior to the 2009 Food and Drug Administration

(FDA) PRO guidance [12] and therefore lack the research dictated by current standards, such as the FDA guidance to collect input from the disease-specific target patient population during instrument development. The well-documented heterogeneity in clinical, radiological, biological and pathological presentations of MS [13] raises the question of whether progressive MS is a separate disease or is a part of the MS disease spectrum [4]; due to this debate, it is unknown whether fatigue PRO instruments developed with data from patients with RRMS are applicable to progressive forms of MS, or if there are differences in presentation of fatigue. Critically, the literature search failed to identify any existing MS-related fatigue PRO instruments that included qualitative feedback from patients with progressive MS in their development. Thus, it is unclear whether existing PRO instruments can appropriately evaluate fatigue in progressive MS. With no current MS therapies with fatigue in their label and no published clinical trials that have studied fatigue in the progressive MS population, there is growing recognition that patient perspectives in progressive MS will be essential to optimally guide management of the disease in clinical practice and evaluation of new therapeutics in clinical trials [14–16].

To start addressing some of these issues and initiate PRO development in patients with progressive MS, this study aimed to (1) obtain qualitative evidence to understand how patients with progressive MS characterize fatigue, as well as how it impacts their HRQoL and daily activities, and (2) determine the conceptual overlap of the progressive MS patient experience with concepts assessed by existing MS-specific fatigue PRO instruments. These findings are valuable for clinical investigators, outcomes specialists, policymakers, healthcare professionals, patient organizations, patients, caregivers and others to guide future work on assessing fatigue-related aspects of progressive MS. Our expectations for the findings were as follows: (1) physical fatigue and mental fatigue are characterized as related but unique concepts by patients with MS, (2) both physical fatigue and mental fatigue are defined by several subdomains or uniquely identifiable characteristics that are agreed upon by several patients, and (3) some of the newer measures of MS-related fatigue are likely to best match the conceptual domains revealed in this study.

## METHODS

The study flowchart is presented in Fig. 1.

### Ethics

The study received approval from the New England Institutional Review Board under the WCG Institutional Review Board (IRB0000053) and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Prior to the collection of any data, participants signed a written informed consent form that was used to outline the

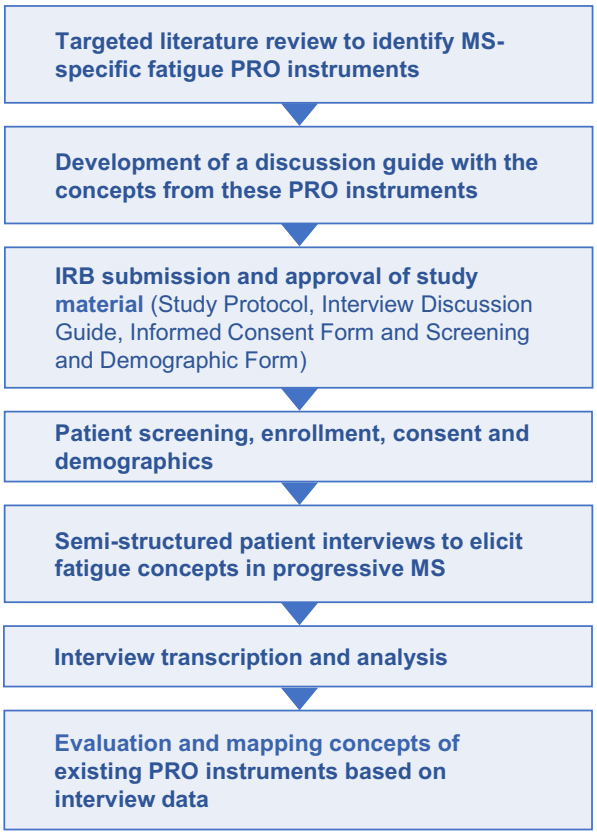


**Fig. 1** Study flowchart. Abbreviations: *IRB* institutional review board, *MS* multiple sclerosis, *PRO* patient-reported outcome

research purpose and confirm their voluntary participation and right to end participation at any moment.

## Recruitment

Thirty participants were recruited via email and telephone from across the United States (US) via physician referrals and an existing database of patients who previously agreed to participate in MS research. Recruitment targets were set purposively to ensure a diverse set of participants, including broad representation across forms of progressive MS (PPMS and SPMS) and across disability levels based on the self-reported disability status scale (SRDSS) [17], a PRO measure of disability that serves to estimate the widely recognized Expanded Disability Status Scale used in MS clinical research [18].

### *Eligibility Criteria*

To meet inclusion criteria, all participants were $\geq$ 18 years of age at the time of screening; had a physician-confirmed PPMS or SPMS diagnosis; reported experiencing MS-related fatigue in the past 6 months; and were determined by the recruiter and moderator to have adequate US English communication and ability to participate in the interview (i.e., understand the informed consent and reflect on their experience with MS-related fatigue in a research session). Exclusion criteria were as follows: diagnosis of major untreated sleep disorder (e.g., sleep apnea); documented head trauma in the past 3 months; documented other neurological or neuropsychiatric disorders that cause fatigue; active infection that causes fatigue; taking any of the following medications that cause excessive daytime sleepiness: high-dose gabapentin (> 600 mg/day), pregabalin, nortriptyline, amitriptyline, opioids for pain management; and currently enrolled in a clinical study/trial. Although the presence or absence of benzodiazepine use was not explicitly part of screening criteria, no participants reported current benzodiazepine use.

## Interviews

Video-conference interviews lasting approximately 60 minutes were conducted with each participant by a trained female moderator with 5 years of qualitative research experience. All patients opted to participate from home. The interview discussion guide in the Supplementary Material Appendix was pilot-tested with a non-patient audience and then used with patient interviews to elicit MS-related fatigue concepts in a semi-structured manner and according to well-regarded guidance from the FDA and ISPOR (The Professional Society for Health Economics and Outcomes Research) [12, 19].

### *Qualitative Analysis*

Audio recordings of the interviews were transcribed verbatim and anonymized. Responses were categorized by the interviewer and a senior qualitative researcher who reviewed the transcripts and results. Data codes were entered and analyzed in MAXQDA version 18.2.0 (VERBI GmbH, Berlin), a qualitative analysis software program. Established qualitative research methods, including grounded theory and constant comparative method, were applied to analyze the interviews for fatigue concepts [20]. A coding scheme to catalogue fatigue concepts was developed based on the concept elicitation discussion guide and research objectives and was updated as necessary to incorporate newly emerging data based on patients' responses.

Qualitative data from the interviews were assessed for conceptual saturation. Saturation is considered to be achieved at the point when additional interviews are unlikely to yield new information (i.e., new concepts of importance and relevance to participants) [21]. Achieving saturation is also an indication that the sample size is adequate, and therefore determining an adequate sample size a priori can be difficult. There is evidence that saturation can be achieved in relatively homogeneous samples as small as 12 participants; however, sample size likely needs to be increased when samples are more heterogeneous or when various subgroup

analyses are desired (e.g., narrow age groups) [22].

In order to evaluate conceptual saturation, concepts spontaneously emerging from the research sessions were analyzed in sets based on the order in which the data were collected. The goal of this process was to compare the amount of novel information that was observed in the first cohort compared to the second cohort and so forth. In addition to highlighting the emergence of new concepts that will allow for the development of a comprehensive list of concepts, saturation also confirms the adequacy of the sample size. Data were assessed for conceptual saturation across the entire sample and for the separate PPMS and SPMS populations.

### Evaluation of PRO Instruments

As part of the preliminary study development, a gap analysis was performed on MS-specific fatigue PRO instruments identified from the literature, and the subset of these PRO instruments with at least partial validation was selected for inclusion in the concept mapping evaluation in this study.

As part of the primary study with patient-reported fatigue concepts, the selected MS-specific fatigue PRO instruments were evaluated for conceptual overlap with the fatigue concepts reported by patients in the qualitative interview research. The level of patient endorsement for each mapped PRO concept was defined by the fraction of the total sample ($n = 30$) reporting the concept, as follows: high endorsement was $> 10$ participants ($> 33.3\%$), medium endorsement was 6–10 participants (20.0−33.3%) and low endorsement was $\leq 5$ participants ($< 20.0\%$).

## RESULTS

Thirty patients with a confirmed diagnosis of progressive MS and fatigue (within 6 months of the study) completed concept elicitation interviews between July 14 and August 14, 2020.

### Demographics

All recruitment targets for a diverse range of demographic and clinical characteristics were met, including sampling across the courses of progressive MS: PPMS ($n = 14$, 46.7%), active SPMS ($n = 10$, 33.3%), and non-active SPMS ($n = 6$, 20.0%). The average length of time since MS diagnosis was 13 years (range 2–34). The average age was 51 years (range 32–75), and there was more female ($n = 21$, 70.0%) than male ($n = 9$, 30.0%) representation. The full patient demographic information is presented in Table 1.

### Characterization of Fatigue by Patients with Progressive MS

Twenty-three unique concepts of fatigue symptoms and 42 concepts of impact of fatigue emerged from interviews with patients with progressive MS; these are reported in detail below. Overall, patients characterized physical and mental concepts of fatigue separately, with most patients ($n = 24$, 80.0%) experiencing both physical and mental features of fatigue.

#### *Concept Saturation Analysis*

Fatigue-related concept saturation for the total progressive MS sample was achieved by the 20th of 30 interviews. These results confirm that collecting additional data will likely not add to the understanding of how patients characterize fatigue in progressive MS. When calculated separately for patients with PPMS or SPMS (including active and non-active combined), all fatigue-related concepts saturate as well, suggesting adequate sample sizes for these subpopulations. Saturation was not calculated separately for the active and non-active SPMS sample given limitations in sample size. As these saturation results indicate comprehensive sampling of fatigue concepts for the total progressive MS population as well as PPMS and SPMS subpopulations, data are reported by these sample groups throughout this study.

**Table 1** Demographic characteristics of study participants

| Characteristic | PPMS ($n$ = 14) | SPMS, active ($n$ = 10) | SPMS, non-active[a] ($n$ = 6) | Total sample ($n$ = 30) |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean | 49.8 | 53.1 | 50.8 | 51.5 |
| Range | 32–68 | 33–75 | 41–58 | 32–75 |
| Gender ($n$, %) | | | | |
| Female | 11 (78.6%) | 6 (60.0%) | 4 (66.7%) | 21 (70.0%) |
| Male | 3 (21.4%) | 4 (40.0%) | 2 (33.3%) | 9 (30.0%) |
| Race/ethnicity ($n$, %) | | | | |
| Caucasian (white, non-Hispanic) | 10 (71.4%) | 6 (60.0%) | 3 (50.0%) | 19 (63.3%) |
| Black or African American | 3 (21.4%) | 3 (30.0%) | 1 (16.7%) | 7 (23.3%) |
| Hispanic/Latino | 1 (7.1%) | – | 1 (16.7%) | 2 (6.7%) |
| Asian | – | 1 (10.0%) | – | 1 (3.3%) |
| Multiethnic[b] | – | – | 1 (16.7%) | 1 (3.3%) |
| Sleep disorder status ($n$, %) | | | | |
| No sleep disorder | 11 (78.6%) | 7 (70.0%) | 5 (83.3%) | 23 (76.7%) |
| Treated insomnia | 2 (14.3%) | 2 (20.0%) | – | 4 (13.3%) |
| Treated sleep apnea | 1 (7.1%) | 1 (10.0%) | 1 (16.7%) | 3 (10.0%) |
| SRDSS score ($n$, %) | | | | |
| $< 3.5$ | 3 (21.4%) | 3 (30.0%) | 1 (16.7%) | 7 (23.3%) |
| 4–6.5 | 10 (71.4%) | 6 (60.0%) | 4 (66.7%) | 20 (66.7%) |
| $> 7$ | 1 (7.1%) | 1 (10.0%) | 1 (16.7%) | 3 (10.0%) |
| Time since MS diagnosis (years) | | | | |
| Mean | 15.5 | 11.1 | 8.4 | 13.4 |
| Minimum–maximum | 2–34 | 2–18 | 2–14 | 2–34 |
| Highest level of education ($n$, %) | | | | |
| High school graduate (or equivalent) | – | 1 (10.0%) | – | 1 (3.3%) |
| Some college (no degree) | 1 (7.1%) | – | 1 (16.7%) | 2 (6.7%) |
| Associate's degree | 3 (21.4%) | 4 (40.0%) | 1 (16.7%) | 7 (23.3%) |
| Bachelor's degree | 10 (71.4%) | 4 (40.0%) | 2 (33.3%) | 16 (53.3%) |
| Master's degree | 1 (7.1%) | 1 (10.0%) | 1 (16.7%) | 3 (10.0%) |

**Table 1** continued

| Characteristic | PPMS ($n$ = 14) | SPMS, active ($n$ = 10) | SPMS, non-active[a] ($n$ = 6) | Total sample ($n$ = 30) |
|---|---|---|---|---|
| Doctoral degree | – | – | 1 (16.7%) | 1 (3.3%) |
| Work status ($n$, %) | | | | |
| On disability | 6 (42.9%) | 3 (30.0%) | 1 (16.7%) | 10 (33.3%) |
| Retired | 1 (7.1%) | 2 (20.0%) | 1 (16.7%) | 4 (13.3%) |
| Unemployed | 1 (7.1%) | 1 (10.0%) | 1 (16.7%) | 3 (10.0%) |
| Working full-time | 6 (42.9%) | 2 (20.0%) | 1 (16.7%) | 9 (30.0%) |
| Working part-time | 1 (7.1%) | 2 (20.0%) | 2 (33.3%) | 5 (16.7%) |
| Student | 1 (7.1%) | – | – | 1 (3.3%) |
| General health status ($n$, %) | | | | |
| Excellent | 2 (14.3%) | 1 (10.0%) | 1 (16.7%) | 4 (13.3%) |
| Very good | 2 (14.3%) | 2 (20.0%) | 1 (16.7%) | 5 (16.7%) |
| Good | 4 (28.6%) | 3 (30.0%) | 3 (50.0%) | 11 (36.7%) |
| Fair | 8 (57.1%) | 3 (30.0%) | 1 (16.7%) | 9 (30.0%) |
| Poor | – | 1 (10.0%) | – | 1 (3.3%) |
| Current treatments (selected all that apply) ($n$, %) | | | | |
| Ocrevus® (ocrelizumab) | 10 (71.4%) | 1 (10.0%) | 1 (16.7%) | 12 (40.0%) |
| None | 2 (14.3%) | 1 (10.0%) | 1 (16.7%) | 5 (16.7%) |
| Copaxone® (glatiramer acetate) | 1 (7.1%) | 2 (20.0%) | – | 3 (10.0%) |
| Tecfidera® (dimethyl fumarate) | 1 (7.1%) | 1 (10.0%) | 1 (16.7%) | 2 (6.7%) |
| Avonex® (interferon β-1a) | – | – | 2 (33.3%) | 2 (6.7%) |
| Betaseron® (interferon β-1b) | – | 2 (20.0%) | – | 2 (6.7%) |
| Aubagio® (teriflunomide) | 1 (7.1%) | – | – | 1 (3.3%) |
| Mavenclad® (cladribine) | – | – | 1 (16.7%) | 1 (3.3%) |

Abbreviations: *MS* multiple sclerosis, *PPMS* primary progressive MS, *SPMS* secondary progressive MS, *SRDSS* self-reported disability status scale

[a]Non-active MS was defined as an individual with no documented clinical or radiological clinical relapses for at least the past 2 years at the time of screening

[b]One patient wrote in "multiethnic" for race/ethnicity

### *Signs and Symptoms of Physical Fatigue*

Figure 2 summarizes concepts of physical fatigue symptoms elicited from patients. Detailed results with exemplary patient quotes for all 23 fatigue-related symptoms including physical fatigue symptoms ($n$ = 12) are presented in Supplementary Material Table S1. All patients ($n$ = 30, 100%) reported experience with

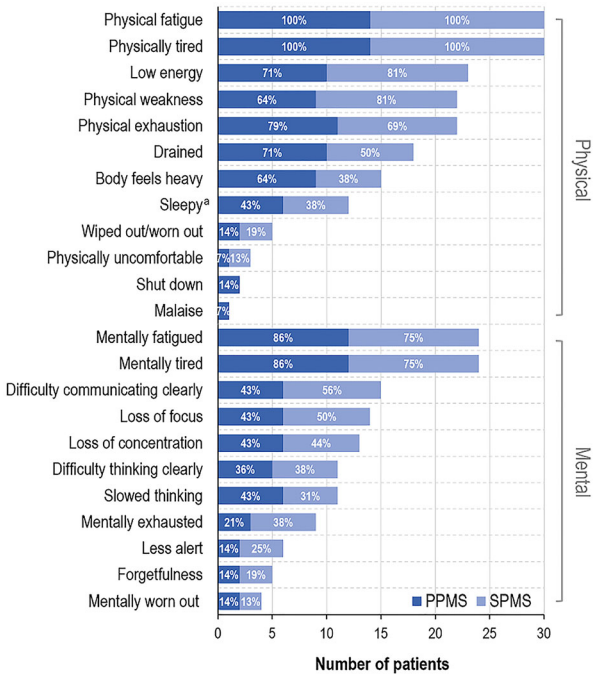


**Fig. 2** Physical and mental fatigue symptoms reported by patients with progressive MS (PPMS and SPMS). Abbreviations: *FSIQ-RMS* Fatigue Severity Impact Questionnaire—Relapsing Multiple Sclerosis, *MS* multiple sclerosis, *PPMS* primary progressive MS, *SPMS* secondary progressive MS. [a]*n* = 12 noted that fatigue did not feel like sleepiness

physical aspects of fatigue and commonly described it using the terms physical fatigue and feeling physically tired.

### *Signs and Symptoms of Mental Fatigue*

Similar to descriptions of physical fatigue, characterizations of mental aspects of fatigue (see Fig. 2 and Supplementary Material Table S1) were referred to as mental fatigue and feeling mentally tired. Most patients (*n* = 24, 80.0%) reported experience with mental aspects of fatigue resulting in difficulty communicating and concentrating or focusing. Six patients reported that they did not experience non-physical aspects of fatigue. A comparison of demographic characteristics showed that those who did not experience mental fatigue had similar average age (50.1 vs. 50.7 years), SRDSS scores and self-reported health category scores as compared with those who did experience mental fatigue.

### *Distinction Between Mental Fatigue and Cognitive Impairments*

Given the overlap between the descriptions of mental fatigue and the known prevalence of cognitive impairments in MS, patients were also asked to characterize their experience with cognitive impairments compared to their experience of fatigue. Half of the patients (*n* = 15, 50.0%) experienced both cognitive disruptions caused by MS and mental components of fatigue. The remaining patients noted that they did not experience cognitive disruptions (*n* = 9, 30.0%), only experienced cognitive disruptions and not mental components of fatigue (*n* = 4, 13.3%), or did not experience either (*n* = 2, 6.7%). When comparing the sample for those who did versus those who did not report experiencing cognitive impairments, both groups had similar average age (51 years), SRDSS scores and self-reported health category scores. Several participants with an underlying cognitive impairment reported that it worsened with fatigue.

### *Dimensions of Fatigue*

Patients were asked to provide data on the frequency, duration and severity of their fatigue. Nearly all patients reported either that fatigue was a daily occurrence (*n* = 24, 80.0%) or that it occurred most days (*n* = 4, 13.3%). Only one patient (3.3%) reported experiencing fatigue less than most days (i.e., on a monthly basis). Patients commonly cited that fatigue lasted several hours (*n* = 15, 50.0%) or was constant (*n* = 11, 36.7%), although a few patients (*n* = 4, 13.3%) noted it lasted less than an hour. All patients who noted their fatigue was less frequent or had shorter duration (*n* = 4, 13.3%) reported a less severe disease state and better self-reported health scores during screening. Patients were asked to rate the severity of fatigue at its worst on an 11-point numeric rating scale ranging from no fatigue (0) to worst fatigue imaginable (10); the average rating was 8.5 (range 4–10). When asked to provide data on what a meaningful improvement would be in

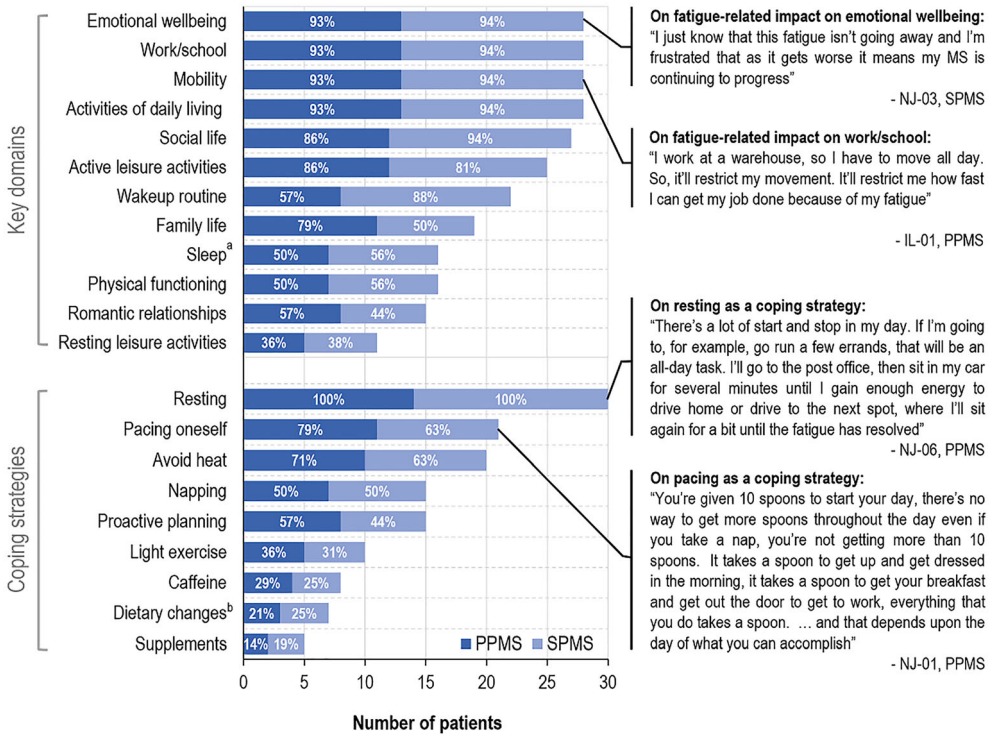


**Fig. 3** Key domains of fatigue-related impacts and coping strategies reported by patients with progressive MS (PPMS and SPMS). Abbreviations: *MS* multiple sclerosis, *PPMS* primary progressive MS, *SPMS* secondary progressive MS. [a]Four of seven patients with a comorbid sleep disorder reported experiencing an impact on sleep (likely exacerbated by fatigue). [b]Patients described dietary changes as improvements to their diet (e.g., cutting out sugar, eating more fruits and vegetables as opposed to processed foods, drinking more water)

terms of their MS-related fatigue, patients provided multiple responses but most frequently noted that improvements in severity ($n$ = 20, 66.7%), frequency ($n$ = 15, 50.0%) or duration ($n$ = 12, 40.0%) of fatigue would be meaningful.

### *Impacts of Fatigue*

Figure 3 summarizes the results by key domains of fatigue-related impacts. Detailed results for all 42 fatigue-related impact concepts across the key domains are presented in Supplementary Material Table S2. When asked about the perceived implications of fatigue on key HRQoL domains, nearly all patients reported negative impacts on emotional well-being ($n$ = 28, 93.3%), work/school ($n$ = 28, 93.3%), mobility ($n$ = 28, 93.3%) and activities of daily living ($n$ = 28, 93.3%).

Among those with negative impacts on emotional well-being, patients most commonly experienced low motivation ($n$ = 24, 80.0%), frustration ($n$ = 20, 66.7%), and depression or sadness ($n$ = 19, 63.3%) because of their MS-related fatigue. Among those feeling frustrated, patients indicated that they felt this way due to concern for their symptoms. Nearly half of patients ($n$ = 14, 46.7%) reported being less efficient or productive at work/school because of fatigue. In terms of mobility impact, most patients ($n$ = 23, 76.7%) reported that they needed to use a mobility aid, experienced difficulty walking ($n$ = 24, 80.0%) or experienced clumsiness ($n$ = 21, 70.0%) because of fatigue. Additionally, several cited having balance issues ($n$ = 14, 46.7%) or having difficulty standing ($n$ = 14, 46.7%) because of their MS-related fatigue.

The activities of daily living category comprised concepts that reflected alterations in patients' abilities to complete everyday tasks.

Nearly all patients ($n$ = 28, 93.3%) reported that their fatigue made it difficult to complete household activities (e.g., chores, cooking). Seventeen patients ($n$ = 17, 56.7%) highlighted difficulty running errands, and many reported that fatigue changed the way they did things (i.e., a modification in the method of completion of daily activities). A small group of patients ($n$ = 6, 20.0%) noted that they had trouble driving when experiencing fatigue.

### *Triggers of Fatigue*

Patients were asked to characterize whether there were specific situations or behaviors that exacerbated their fatigue. All, or nearly all, patients identified physical exertion ($n$ = 30, 100.0%) and high temperature or heat ($n$ = 29, 96.7%) as triggers of fatigue. Although all patients were able to provide specific scenarios where something caused fatigue, much of the sample ($n$ = 22, 73.3%) also commented that fatigue occurred without any external influencing factor. Other reported triggers included experiencing fatigue at the midpoint of the day or after lunch ($n$ = 20, 66.7%) or during stressful events ($n$ = 2, 6.7%).

### *Coping Strategies for Fatigue*

Figure 3 summarizes the fatigue-related coping strategies reported by study participants. When asked to characterize how they managed their fatigue, a majority of the patients ($n$ = 19, 63.3%) reported that they had never taken any medication specifically to assist with fatigue; however, 36.7% ($n$ = 11) highlighted that they had received a prescription treatment (e.g., stimulant) to alleviate the severity of their fatigue. Most patients who had received treatment ($n$ = 9 of 11, 81.8%) reported that it was ineffective in helping to manage their fatigue. All patients ($n$ = 30, 100.0%) noted that they helped manage their fatigue by resting frequently. Similarly, most patients ($n$ = 21, 70.0%) commented that they paced themselves through their activities to better manage their fatigue, and routine activities were selected based on their fatigue for a given day.

## Evaluation of Existing PRO Instruments

The literature review identified 14 existing MS-specific fatigue PRO instruments, with the following five having some level of qualitative or quantitative research performed to validate their use for fatigue assessment in an MS population: Modified Fatigue Impact Scale (MFIS) [23], Fatigue Severity Scale (FSS) [24], Fatigue Symptoms and Impacts Questionnaire—Relapsing Multiple Sclerosis (FSIQ-RMS) [25], Quality of Life in Neurological Disorders Fatigue Scale (Neuro-QoL FS) [26] and Functional Assessment of MS (FAMS) [27].

PRO instruments were evaluated for their relevance in a progressive MS population based on the overlap of concepts in the PRO instruments with concepts reported in the qualitative interviews, plus—based on the interview results—a criterion for assessment of both physical and mental aspects of fatigue was considered. The FSS, Neuro-QoL FS, and FAMS were assessed as having low suitability, as they omit key concepts reported by the progressive MS population in this study and/or do not distinguish between mental and physical aspects of fatigue. The FSIQ-RMS and MFIS met all preliminary mapping criteria and are evaluated in detail below.

### *Evaluation: MFIS*

Several favorable characteristics and some limitations of the MFIS were identified. Like the FSIQ-RMS, the MFIS distinguishes between mental and physical fatigue characteristics and associated implications. The MFIS received high levels of patient endorsement for most items. However, highly endorsed concepts from the qualitative research, such as tiredness, are not included in this PRO instrument. Furthermore, the MFIS received low or no patient endorsement for several concepts, including difficulty making decisions, forgetfulness and physical discomfort.

Modifications may be necessary to include the additional highly endorsed concepts and to eliminate items with no relevance to the progressive MS population. Additionally, the MFIS was not developed in accordance with the FDA

PRO guidance and did not have any MS patient input prior to development; this may require further adaptation to be validated according to the guidance. Overall, the MFIS was found to be suitable for progressive MS contingent on modifications.

***Evaluation: FSIQ-RMS***

Several favorable characteristics of the FSIQ-RMS were identified. First, the conceptual framework of the FSIQ-RMS encompasses a holistic set of concepts that assess MS-related fatigue across domains of symptoms and impacts, including impacts on coping strategies. Importantly, FSIQ-RMS separates between mental and physical fatigue characteristics and associated implications. Furthermore, the FSIQ-RMS was developed in accordance with the FDA PRO guidance.

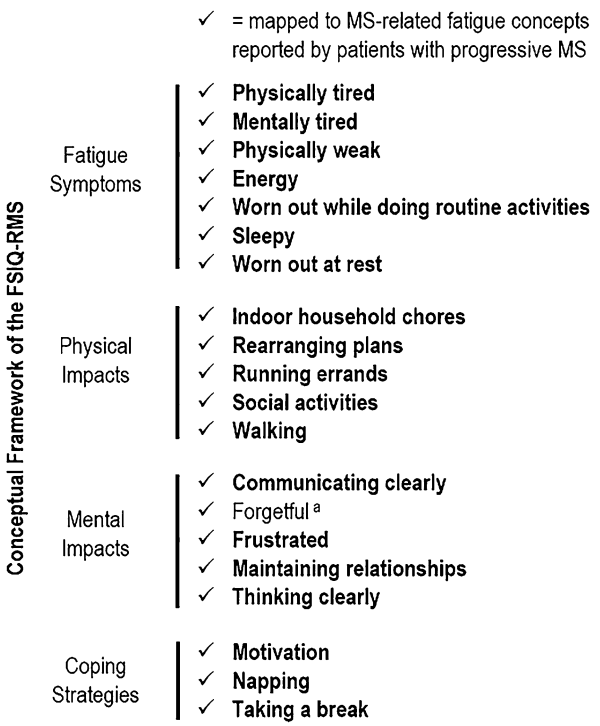


**Fig. 4** Concept mapping of the FSIQ-RMS to the patient experience of fatigue in progressive MS. Abbreviations: *FSIQ-RMS* Fatigue Severity Impact Questionnaire—Relapsing Multiple Sclerosis, *MS* multiple sclerosis. [a]All FSIQ-RMS concepts were highly endorsed (bold font) by study participants, except forgetfulness, which received low endorsement

All 20 concepts assessed by this instrument mapped to the MS-related fatigue concepts reported by the progressive MS population in this study (Fig. 4). The FSIQ-RMS concepts received a high level of patient endorsement for 19 of 20 concepts, including key symptoms of MS-related fatigue. The only FSIQ-RMS fatigue-related concept to receive low patient endorsement was forgetfulness (see Fig. 2). Overall, the FSIQ-RMS was found to be the most suitable of the existing PRO instruments for assessing MS-related fatigue in progressive MS.

## DISCUSSION

This research obtained much-needed evidence from patients with progressive MS to understand the important symptoms and impacts of MS-related fatigue. The fatigue concepts reported by the study participants were mapped to the conceptual frameworks of existing PRO instruments to determine which instruments best measure MS-related fatigue in the progressive MS population.

### Patient-Centered Fatigue Concepts in Progressive MS

As concept saturation was met for the total study population as well as PPMS and SPMS separately, the sample size can be considered sufficient to comprehensively capture fatigue concepts in both PPMS and SPMS. Fatigue concepts were similar between PPMS and SPMS populations, with all highly endorsed concepts represented and the level of concept endorsement trending similarly in both populations. Patients with progressive MS characterized fatigue as a multidimensional concept that contains both physical and mental aspects. While the experience of physical fatigue was universal, aspects of mental fatigue were not reported by some ($n$ = 6) patients; therefore, physical and mental concepts should be assessed separately. Patients characterized mental fatigue as distinct from cognitive impairment, with nearly a third reporting mental fatigue without cognitive disruption and several reporting cognitive disruption without mental fatigue.

Fatigue creates a high degree of burden for patients with progressive MS, with most experiencing fatigue daily and for several hours or constantly; patients rated "severity of fatigue at its worst" as high (scoring an average of 8.5 on a scale of 0–10, with 10 being the highest). Patients also reported widespread consequences of fatigue across all key HRQoL domains, with almost all patients (≥ 90%) experiencing negative impacts on emotional well-being, work/school, mobility and activities of daily living; only one key HRQoL domain, resting leisure activities, was impacted for less than half of patients. These data underline a significant unmet need for effective treatment of fatigue in the progressive MS population, particularly given the severe burden of fatigue despite most participants taking medication to treat MS. These results expand the current understanding of the patient experience of fatigue in progressive MS and are consistent with the existing, but limited, body of literature [11, 28]. Further, these interview data suggest that treatments for MS should aim to improve concepts of fatigue symptoms and impacts that patients find to be clinically meaningful—including separate mental and physical concepts—as well as address the dimensions of fatigue (frequency, duration and severity) that can negatively impact patients' everyday lives and impair HRQoL. This study is at the beginning of the methodical PRO development process outlined by the FDA's PRO guidance [12]. This qualitative stage is a valuable and necessary step for understanding the patient experience. After this study, additional psychometric analyses will be needed to confirm this conceptual framework's fit with obtained data.

## Evaluation of Existing Fatigue PRO Instruments in Progressive MS

We analyzed the conceptual overlap of the concept elicitation research with existing PRO instruments used to evaluate fatigue in MS and identified some value as well as shortcomings of several instruments. Some PRO instruments omit key concepts and/or do not distinguish between mental and physical aspects of fatigue, such as the FSS, Neuro-QoL FS, and FAMS. The MFIS would need some revisions to fully assess key concepts of fatigue in patients with progressive MS. The FSIQ-RMS has been validated, including qualitative and quantitative (i.e., psychometrics) approaches, in an active MS population. This instrument has not been validated in a progressive population, though a small pilot sample in the study suggested the potential for broader applicability of the FSIQ-RMS with additional research [25]. The concepts from this study provide preliminary support of the appropriateness and relevance of the FSIQ-RMS in assessing fatigue in patients with progressive MS (PPMS and SPMS). Additional qualitative and quantitative research studies (i.e., cognitive interviews and psychometrics) are needed to further evaluate and validate the FSIQ-RMS in the progressive MS population. More broadly, this study demonstrates how existing PRO instruments can potentially offer viable alternatives to de novo PRO instrument development for measuring patient-reported concepts.

## Study Strengths, Limitations and Future Directions

With the individual interview study design, participants had an opportunity to discuss their experience at length and provided a depth of data that is difficult to collect using other research methods. Despite this strength, the ability to generalize the data to the overall MS population is limited, as the sample includes only individuals with recent fatigue experience as part of the eligibility criteria; thus, study results on the degree to which fatigue was bothersome should be interpreted within this context. Due to the COVID-19 pandemic, video conference calls were conducted instead of in-person interviews, which may have hidden some body language and other nonverbal information. Another consideration is that although the eligibility criteria excluded patients with neurological or neuropsychiatric disorders, half of patients self-reported experience with cognitive impairments and could be considered less reliable reporters. This is a

qualitative study to identify fatigue concepts and was not designed to quantify differences between populations (i.e., PPMS and SPMS), clinical characteristics or outcomes; thus, numerical differences should be interpreted with caution. Additional topics that may be explored in future studies include whether fatigue severity correlates with duration of MS diagnosis, level of physical disability, age or presence of other MS symptom management therapies such as baclofen. The developmental work in this study sets the stage for future work to validate existing PRO instruments for fatigue assessment in the progressive MS population.

## CONCLUSION

This qualitative study of a progressive MS population combined a patient-centric approach with robust methods of qualitative data analysis to gain a greater understanding of the key concepts, humanistic burden and impact of MS-related fatigue in this population. Meaningful physical and mental components of MS-related fatigue were identified in the progressive MS population. Most patients reported daily fatigue occurring for several hours a day and experienced fatigue-related negative impacts on HRQoL for nearly all activities. Evaluation of existing PRO instruments used to assess fatigue in MS showed that many had conceptual gaps for patients with progressive MS or did not distinguish between physical and mental concepts of fatigue. The FSIQ-RMS was deemed the most appropriate for assessing fatigue in patients with progressive MS, based on concordance with the qualitative data collected from this research study; this supports similar fatigue concepts and presentation among patients with relapsing MS and patients with progressive MS. Further evaluation in the progressive MS population for content validity and validation is warranted. Future modifications to the FSIQ-RMS may be needed to capture all aspects of fatigue experienced and reported by patients with progressive MS. Taken together, these results provide clear evidence that there is a high unmet need among the progressive MS population to address MS-related fatigue from the patient perspective.

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***Disclosures.*** Crystal Watson, Arie Barlev and Kiren Kresa-Reahl are employees and shareholders of Atara Biotherapeutics. Kayla Scippa and Jason C. Cole were employees of ZS Associates during this study. Jason C. Cole is an employee of P3 Research Consulting, Torrance, CA, USA. Kayla Scippa is an employee of Janssen Research & Development LLC, Raritan, NJ.

***Compliance with Ethics Guidelines.*** The study received approval from the New England Institutional Review Board under the WCG Institutional Review Board (IRB0000053) and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Prior to the collection of any data, participants signed a written Informed Consent Form that was used to outline the research purpose and confirm their voluntary participation and right to end participation at any moment.

***Data Availability.*** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request and within the informed consent. The data are not publicly available due to them containing information that could compromise research participant privacy/consent.



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