Examining Fatigue in Progressive Multiple Sclerosis: Results from a Qualitative Study and Review of Patient-reported Outcomes (PRO) Measures

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Poster #QOL09

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BACKGROUND

- Fatigue is one of the most common and debilitating symptoms of MS, occurring in approximately 80% of people diagnosed with the disease[1]
- Assessment of fatigue has proven difficult as the symptom is complex, its pathophysiology is not well understood, and there is no clear consensus for a definition of fatigue[2,3]
- Several PRO instruments assess MS-related fatigue;[4,5] however, few PROs include the perspective of patients with progressive MS in their development[6,7]
- Understanding fatigue in progressive MS is important, given that patients with PPMS and SPMS experience continued worsening of neurologic impairments[8-10]

OBJECTIVE

- This qualitative study was conducted to understand fatigue in a progressive MS population and to evaluate the conceptual frameworks of existing MS-specific PRO instruments for use in this population

METHODS

Methodology

- A targeted literature review identified MS-specific fatigue PROs
- A discussion guide was developed with the concepts from these PROs
- The protocol, discussion guide and consent form were submitted and IRB-approved
- Patients were screened and provided consent
- Semi-structured interviews were conducted with 30 US adult participants who met the inclusion/exclusion criteria and participated in video-conference interviews to elicit MS-related fatigue concepts
- Data were analyzed and compared with concepts in PRO instruments to evaluate their relevance in a progressive MS population

Key Eligibility Criteria*

- **Inclusion criteria**: ≥18 years of age at the time of screening; physician-confirmed diagnosis of either PPMS or SPMS; reported experiencing MS-related fatigue in the past 6 months
- **Exclusion criteria**: Diagnosis of major untreated sleep disorder (eg, sleep apnea); documented head trauma in the past 3 months; documented other neurologic 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; currently enrolled in a clinical study/clinical trial

*Participants were included in qualitative research based on these eligibility criteria; additional recruitment quotas were set for MS type and SRDSS score. SRDSS is a PRO measure that serves to estimate the widely recognized EDSS commonly used in MS clinical research

RESULTS

Figure 1. Study Population/Demographics

- Thirty participants with a confirmed diagnosis of PPMS or SPMS completed concept elicitation interviews between July 14 and August 14, 2020
- All participants reported that fatigue had physical components, described commonly as feeling tired, weak, exhausted, or having low energy[11]
- Most participants (n=24) noted that fatigue had mental components, including difficulty communicating, concentrating, or focusing[11]

*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. †PRO measure that serves to estimate the widely recognized EDSS commonly used in MS clinical research. ‡Participants wrote in "multiethnic" when asked to select race/ethnicity. §Participants selected "student" or "unemployed" when asked to provide work status

MS clinical type*
PPMS: n=14, 46.7%
Active SPMS: n=10, 33.3%
Non-active SPMS: n=6, 20.0%

SRDSS score†
<3.5: n=7, 23.3%
4–6.5: n=20, 66.7%
>7: n=3, 10.0%

Sex
Female: n=21, 70.0%
Male: n=9, 30.0%

Race/ethnicity
Caucasian: n=19, 63.3%
Black/African American: n=7, 23.3%
Hispanic/Latino: n=2, 6.7%
Asian: n=1, 3.3%
Other‡: n=1, 3.3%

Average age and progressive diagnosis length (min–max)
Age: 51.5 years (32–75)
Diagnosis: 13.4 years (2–34)

Self-reported health status
Excellent: n=4, 13.3%
Very good: n=5, 16.7%
Good: n=11, 36.7%
Fair: n=9, 30.0%
Poor: n=1, 3.3%

Work status
On disability: n=10, 33.3%
Working full time: n=9, 30.0%
Working part time: n=5, 16.7%
Retired: n=4, 13.3%
Other§: n=2, 6.7%

Education status
High school graduate: n=1, 3.3%
Some college (no degree): n=2, 6.7%
Associate degree: n=7, 23.3%
Bachelor's degree or higher: n=20, 66.7%

Figure 2. Fatigue Concepts Assessed

- The criteria outlined below were used to compare the concepts mentioned in the primary research with the concepts in the MS-specific fatigue instruments

Preliminary Criteria:

1. Was the concept mentioned at all in primary research?
2. *[If yes],* what level of patient endorsement did the concept receive?

PROs mapped (n=5)

- Modified Fatigue Inventory Scale (**MFIS**)
- Fatigue Severity Impact Questionnaire-Relapsing Multiple Sclerosis (**FSIQ-RMS**)
- Fatigue Severity Scale (**FSS**)
- Quality of Life in Neurological Disorders Fatigue Scale (**NeuroQoL FS**)
- Functional Assessment of MS (**FAMS**)

PRO instruments that have low suitability as they omit key concepts and/or do not distinguish between mental and physical aspects of fatigue

- FSS
- NeuroQoL FS
- FAMS

PRO instruments that meet all mapping criteria

- MFIS
- FSIQ-RMS

Table 1. PRO Concept Review: FSIQ-RMS

Favorable characteristics

- **Separates between mental and physical fatigue** characteristics and associated implications
- **High level of patient endorsement** for nearly all items
- Developed post-**2009 FDA PRO guidance** and aligns with key recommendations for pursuit of a labeling claim

Overall, the FSIQ-RMS was found to be most suitable for progressive MS

Level of patient endorsement
(for Tables 1 and 2)

High: n>10 participants (>33%)
Medium: n=6–10 participants (20–33%)
Low: n≤ 5 participants (<20%)
N/A: not endorsed

Concepts assessed by the FSIQ-RMS. (7-day symptom recall and 11-point NRS, 4-week impact recall and 5-point VDS scales)

Key concept	Mentioned by participants	Level of endorsement
Energy	✓	High
Mentally tired	✓	High
Physically tired	✓	High
Physically weak	✓	High
Sleepy	✓	High*
Worn out with activities	✓	High
Worn out at rest	✓	High
Indoor/household chores	✓	High
Rearranging plans	✓	High
Running errands	✓	High
Social activities	✓	High
Walking	✓	High
Communicating clearly	✓	High
Forgetful	✓	Low
Frustrated	✓	High
Maintaining relationships	✓	High
Thinking clearly	✓	High
Motivation	✓	High
Napping	✓	High
Taking a break	✓	High

*n=12 participants noted that they would not include sleepiness as a descriptor of fatigue

Table 2. PRO Concept Review: MFIS

Favorable characteristics

- **Separates between mental and physical fatigue** characteristics and associated implications
- **High level of patient endorsement** for most items

Additional considerations

- Highly endorsed concepts, such as **physical fatigue and tiredness, are not included** in the PRO
- **Modifications may be necessary** to include the highly endorsed concepts and eliminate items with low or no relevance to the progressive MS population
- **Developed prior to 2009 FDA PRO guidance** so may experience challenges if pursuing labeling claim without modifications

Concepts assessed by the MFIS. Because of my fatigue during the past 4 weeks…(Never/Almost Always)

Item (**bolded key concept**)	Mentioned by participants	Level of endorsement
I have been **less alert**	✓	Medium
I have had **difficulty paying attention** for long periods of time	✓	High
I have been **unable to think clearly**	✓	High
I have been **clumsy** and **uncoordinated**	✓	High
I have been **forgetful**	✓	Low
I have had to **pace myself** in my physical activities	✓	High
I have been **less motivated** to do anything that requires **physical effort**	✓	High
I have been **less motivated** to participate in **social activities**	✓	High
I have been limited in my ability to **do things away from home**	✓	High
I have trouble **maintaining physical effort** for long periods	✓	High
I have had **difficulty making decisions**	•	N/A
I have been **less motivated** to do anything that requires **thinking**	✓	High
My **muscles have felt weak**	✓	High
I have been **physically uncomfortable**	✓	Low
I have had **trouble finishing tasks** that **require thinking**	✓	High
I have had **difficulty organizing my thoughts** when doing things at home or at work	✓	High
I have been **less able** to complete tasks that require **physical effort**	✓	High
My **thinking has been slowed down**	✓	High
I have had **trouble concentrating**	✓	High
I have **limited my physical activities**	✓	High
I have needed to **rest more often** or for longer periods	✓	High

Overall, the MFIS is contingent on modifications in order to be suitable for progressive MS

CONCLUSIONS

- **Meaningful physical and mental components of fatigue were identified in a progressive MS population**
- **Some patients had physical fatigue without mental fatigue; therefore, these concepts should be separate**
- **Some PRO instruments omit key concepts and/or do not distinguish between mental and physical aspects of fatigue, such as the FSS, NeuroQoL FS, and FAMS**
- **The MFIS would need some revisions to fully assess key concepts of fatigue in patients with progressive MS**
- **The concepts from this study provide preliminary support of the appropriateness of the FSIQ-RMS in assessing fatigue in patients with progressive MS**

ABBREVIATIONS

EDSS = Expanded Disease Status Scale; FAMS = Functional Assessment of MS; FDA = Food and Drug Administration; FSIQ-RMS = Fatigue Severity Impact Questionnaire-Relapsing MS; FSS = Fatigue Severity Scale; IRB = Institutional Review Board; MS = multiple sclerosis; MFIS = Modified Fatigue Inventory Scale; NeuroQoL FS = Quality of Life in Neurological Disorders Fatigue Scale; NRS = numeric rating scale; PPMS = primary progressive MS; PRO = patient-reported outcome; SPMS = secondary progressive MS; SRDSS = self-reported disability status scale; VDS = verbal descriptor scale

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