**Patient-Reported Outcomes Measures for Multiple Sclerosis: Patient Insights on Fatigue, Cognition, Pain, Depression, and their Interconnectivity**

**Authors:** Tanuja Chitnis,¹ Trishna Bharadia,² Giampaolo Brichetto,³ Andrew Lloyd,⁴ Piet Eelen,⁴ Birgit Bauer,⁵ Hollie Schmidt,⁶ Miriam King,⁶ Jo Vandercappellen,⁶ Jeremy Hobart⁷

**Affiliations:** ¹Brigham and Women’s Hospital, Department of Neurology, Boston, MA, USA, ²Marlow, Buckinghamshire, United Kingdom, ³Associazione Italiana Sclerosi Multipla Rehabilitation Center, Genoa, Italy, ⁴Acaster Lloyd Consulting Ltd, London, United Kingdom, ⁵National Multiple Sclerosis Center of Melsbroek, Melsbroek, Belgium, ⁶Manufacturer for Antworten UG, Abensberg, Germany, ⁷Accelerated Cure Project for Multiple Sclerosis, Waltham, MA, USA, ²Novartis Pharma AG, Basel, Switzerland, ³Pennesinsula Schools of Medicine and Dentistry, University of Plymouth, Plymouth, United Kingdom. ⁶Equally contributing authors

---

**Introduction**

1. Fatigue, cognitive impairment, depression, and pain are highly prevalent symptoms in multiple sclerosis (MS) and can negatively impact quality of life (QoL).

2. These symptoms often co-occur and are interconnected.

3. A better understanding of the interconnected nature of these symptom domains, as well as potential associated underlying biological mechanisms, may help inform the development of targeted behavioral and pharmacological interventions.

4. Furthermore, such knowledge may help to inform the development of patient-reported outcome (PRO) measures that capture the experience of PROMS in more accurate and meaningful ways than existing measures.

**Objectives**

1. To characterize the co-occurrence of fatigue, cognitive impairment, depression, and pain among a large sample of PROMS, and the impact of these symptoms on quality of life.

2. To elucidate insights from a group of MS patient experts on the interconnected nature of fatigue, cognitive impairment, depression, and pain on their experience of PROMS.

3. To identify patients expressing the interconnected nature of fatigue, cognitive impairment, depression, and pain in PROMS, based on a literature review.

**Methods**

**Living Like You (LLY) Survey**

- **Online survey of 2,052 PROMS from 23 different countries.
- **Participants:** respondents to the following questions using a 5-point Likert scale, whereby 1 represented “not at all impactful” and 5 represented “extremely impactful.”

**Objective**

- **Sleep**: the impact of cognitive and physical aspects of sleep on patients’ daily life.

**Survey findings**

- **Fatigue (13%)**
- **Non-specific mental function (12%)**
- **Sleep (16%)**
- **Pain (14%)**

- **Conclusion:**

**Patient insights on symptom domain interconnectivity**

- **Of the 25 patient experts that took part in the interviews and focus groups, 24/25 (96%) were white, 24/25 (96%) had RRMS, and 1 had SPMS.

- **Key patient experts on symptom interconnectivity include:**

  - **Fatigue:**
    - **Fatigue makes it difficult to manage emotions.
    - **Cognitive impairment:**
      - The memory of previous cognitive abilities and fear of future decline can bring on feelings of depression.
    - **Depression:**
      - Fatigue, pain, and cognitive impairment all contribute to feelings of depression.
    - **Pain:**
      - There is a clear relationship between fatigue and pain.

- **A selection of quotes from the patient experts are presented in Figure 2 to demonstrate their experiences of how the four symptoms are interconnected.**

**Literature search**

- **A literature search aimed to identify published articles containing information on biological processes associated with the interconnectedness between symptoms of fatigue, cognitive impairment, depression, and pain in PROMS.**

**Objectives**

- **PubMed was searched across the last 10 years using the following terms:**
  - [(cognition AND fatigue) OR (cognition AND depression) OR (cognition AND fatigue and depression) OR (cognition AND fatigue and pain) OR (cognition AND pain and depression)]
  - “Multiple Sclerosis”
  - “Cognition”
  - “Fatigue”
  - “Depression”
  - “Pain”
  - “Quality of life (QoL)”

**Objective**

- **These biological processes may also be mediated via sleep and specific hormones, such as melatonin and cortisol.**

**Discussion & Conclusions**

- **While recognizing the limitations of the methods used, our findings provide 18% (72%) of PROMS patients with comorbid fatigue, pain, and depression in PROMS impacting QoL, as well as setting the groundwork for future investigations of unifying biological processes driving symptom interconnectivity.**

- **In a large international sample of PROMS, more than half of respondents reported the co-occurrence of symptoms that had an impact on more than one domain.**

- **Qualitative information from interviews/focus groups further contextualized the nature of symptom interconnectivity.**

- **Literature search findings identified three potential biological processes driving the interconnectedness of symptoms.**

- **While this preliminary investigation into symptom interconnectivity provides a starting point for future work, much research is required before definitive answers can be found regarding the biological underpinnings, including:**

  - **Studying sub-groups of PROMS who experience some, none, or all of the symptoms in question, to identify biological differences between these groups.**
  - **Ensuring that existing PRO measures are designed, validated, and fit for purpose to assess the symptoms in question.**
  - **Ensuring that independent symptom domains (e.g., fatigue) and biological outcomes are collected in future studies to allow robust investigation into the associations between these variables.**

**New developing PROs where gaps exist, that are based on well-defined conceptual frameworks**

**Biological processes underpinning symptom interconnectivity**

**Literature search findings**

- **Three key mechanisms implicated in symptom interconnectivity (Figure 3):**

  1. Neuroanatomical changes: MS is associated with changes in structure, function, activity, and connectivity of a wide variety of brain regions. Resultant cortical reorganisation to mitigate effects of damage leads to the breakdown of neural networks
  2. Inflammation: Cytokines and microglial play an important role in MS pathology. Changes in cytokines and T cells in blood and cerebrospinal fluid are associated with fatigue, cognitive impairment, depression, and pain. Microglia in lesions are associated with cognitive impairment, while microglia in the hippocampus are associated with depression. Microglia also play a pivotal role in the development of neuropathic pain
  3. Monoamine disorder: MS-related neurodegeneration may disrupt regions involved in the synthesis and/or release of monoamines, and pro-inflammatory cytokines interfere with the synthesis, release, and uptake of serotonin and dopamine. Fatigue and depression in PROMS may be associated with alterations in noradrenaline and serotonin transporters

**These biological processes may also be mediated via sleep and the hypothalamic-pituitary-adrenal (HPA) axis.**

**Figure 1. Co-occurrence of symptoms impacting QoL in PROMS**

**Figure 2. Patient expert quotes demonstrating symptom interconnectivity**

**Figure 3. Biological processes underpinning symptom interconnectivity**

---

**References**


**Disclosures**

**TC:** Received compensation for consulting from Bogen, Novartis, Roche Genetech, & Sanfil Genzyme. Received research support from the National Institutes of Health, National MS Society, US Department of Defense, Farmaceutici Faisani Srl, and National MS Society, Europe. Received honoraria, support to attend meetings or research support from Abbvie, Acorda, Amgen, Genentech, & Sanofi Genzyme. Received compensation for consulting from Celgene, and Accelerated Cure Project for multiple sclerosis. ELS has served as a member of advisory board of Novartis and Roche. AL receives compensation for consulting from Biogen, Merck, and Sanofi. MS and LM receive honoraria, support to attend meetings or research support from Biogen, Merck, and Genentech. ELS and AL receive honoraria, support to attend meetings or research support from Biogen, Merck, and Sanofi. MS and LM receive honoraria, support to attend meetings or research support from Biogen, Merck, and Genentech. ELS and AL receive compensation for consulting from Celgene, and Accelerated Cure Project has received grants, collaboration funding and consulting payments from Biogen, BMS, and Genentech for participation in research activities. From R&D: SL, et al. 2020;39:1025-32. SL, et al. 2021;30:1061-71.

**Acknowledgements**

**Medical writing support was provided by David McNair, PhD, Novartis CONEXTEC, UK. The final responsibility for the content lies with the authors.**

**Postdoctoral Fellowship**

**Disclosure**

This study was sponsored by Novartis Pharma AG, Basel, Switzerland. Copyright © 2021 Novartis Pharma AG. All rights reserved.

---

**Copyright © 2021 Novartis Pharma AG. All rights reserved.**