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The value of patient-reported outcome measures for multiple sclerosis

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Clinical trials and regulatory agencies historically have focused on clinical outcomes including clinician rated disability measures, biomarkers, and imaging. These outcomes often incompletely measure the experience of patients with their disease. To address these gaps, patient-reported outcome measures (PROMs) were developed to quantify the patient perspective. Although the unique benefit of PROMs has been appreciated there remains uncertainty regarding interpretation and clinical impact of these measures.[1]

This issue of *Multiple Sclerosis Journal* features a study investigating the performance of PROMs in secondary progressive multiple sclerosis (SPMS).[2] Strijbis et al utilized data from the phase 3 randomized, double-blind placebo-controlled ASCEND trial that evaluated the use of natalizumab in a secondary progressive population.[3] During this trial the participants completed the Multiple Sclerosis Impact Scale (MSIS-29) and Medical Outcomes Study Short Form Health Survey (SF-36), which are two widely utilized PROMs. The SF-36 is a generic measure to assess health-related quality of life (HRQOL); whereas the MSIS-29 is a condition-specific PROM evaluating perceived physical and psychological impact of MS. The study presented in this MSJ issue aimed to evaluate the performance of these PROMs over 2 years, as compared to two clinical measures of physical disability, the Expanded Disability Status Scale (EDSS) and Timed-25-foot-walk (T25FW). The primary finding of this study was minimal and inconsistent change was observed over 2 years (MSIS-29 physical 50.8 vs 50.5; MSIS psychological 39.1 vs 36.7; SF-36 physical 33.3 vs 33.5; SF-36 mental 47.0 vs 47.7 for all baseline and week 96 scores), compared to consistent worsening on EDSS and T25FW. Given the inconsistent change the authors cautioned the use of PROMs as a primary outcome in SPMS trials and suggest the need for a re-evaluation of how these measures are utilized longitudinally.

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This study highlights the limitations in our current use of PROMs in all forms of MS. Although the general conclusions are appropriate, there are several limitations to the study and areas that require further research to better define the role of PROMs in MS.

The main areas of concern are the variability and lack of consistent change across patients in the PROMs. Two observations were made by the authors regarding variability of change across time and groups of patients. First, the study found that the proportion of participants with significant worsening from baseline to 24 weeks was more than the change observed after 24 weeks. Second, the proportion of patients with significant improvement at 96 weeks was more than the proportion of patients with significant worsening. These two observations may be explained by response shift. Response shift occurs when an individual's internal standard changes over time; therefore the magnitude of change detected can be obscured due to this adaptive process. This phenomenon has been well described in diseases with unpredictable disease courses and proposed as an explanation for the discrepancy between disability level and patient-reported HRQOL[4]. A study in MS reported 20% of patients demonstrated response shift, with a higher percentage in progressive types, leading to misleading interpretations for SF-36 change scores.[5] Lack of group-level change could also be attributed to how patients internalize and respond to PROMs. Individuals' ratings reflect their frame of reference, whether comparing their health to people with the same diagnosis or others without their diagnosis, or whether their expectations are based on their past health or their ideal health. A study of physical and mental HRQOL in MS demonstrated these appraisal processes explained a large amount of variation in individual scores, and concluded HRQOL should not be assessed without measuring appraisal in MS patients.[6] These observations suggest a universal threshold for meaningful change in PROMs is unlikely to be effective.

In this study significant change was defined only at the group-level. Although multiple thresholds were explored, the underlying assumption was still that a single change measure was applied to the entire population. Minimal important differences (MIDs) have also been shown to vary depending on baseline severity and domain. For patients with good HRQOL at baseline, there will be less ability to reach MID thresholds. This may be an issue with SF-36 mental in this study, where scores are similar to the general US population. Using group-level change can also lead to misclassification bias since larger change is needed at the individual-level due to the larger standard errors associated with individual-change estimates. Reliable change indices or conditional minimal detectable change indices can be calculated at the individual-level to identify meaningful change.[7,8] Although this approach would ensure change exceeds measurement error, it does not indicate whether the change is clinically meaningful. When being used for individual treatment decision-making, considerations surrounding patient values of treatment options and symptoms must be weighed. More research is necessary to determine the optimal way to define a treatment benefit at the individual-level. MS is a disease with significant variability between patients; therefore adopting an individual meaningful change approach should be considered.

Lastly, what patients and clinicians want to measure needs to be defined, and PROMs should be selected based on domains the interventions are addressing. In the study presented the authors chose to compare change in PROMs with the physical disability measures of

EDSS and T25FW. Although these are important physical measures it is likely PROMs are measuring different aspects of health and it is not surprising that change in the two measures is not well correlated. PROMs provide measurement of outcomes not well assessed by current objective neurological outcomes such as EDSS, and provide complementary yet distinct information. The role of PROMs in clinical trials will likely be to focus on features such as mental health, fatigue, and pain that are difficult to quantify with a neurological exam.[9]

We agree with the authors that the use of PROMs as primary outcomes in SPMS trials is unlikely. Several aspects of their use and interpretation need to be clarified for success. Overall, PROMs provide a unique evaluation of the patient experience and there is a need to improve the utilization of these measures to optimize their use in MS.

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Declaration of Conflicting Interests

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