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Patient-reported outcomes in multiple sclerosis: Relationships among existing scales and the development of a brief measure

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ABSTRACT

Several patient-reported outcome (PRO) measures are commonly used in multiple sclerosis (MS) research, but the relationship among items across measures is uncertain. We proposed to evaluate the associations between items from a standard battery of PRO measures used in MS research and to develop a brief, reliable and valid instrument measure by combining these items into a single measure. Subjects ($N=537$) enrolled in CLIMB complete a PRO battery that includes the Center for Epidemiologic Studies Depression Scale, Medical Outcomes Study Modified Social Support Survey, Modified Fatigue Impact Scale and Multiple Sclerosis Quality of Life-54. Subjects were randomly divided into two samples: calibration ($n=269$) and validation ($n=268$). In the calibration sample, an Exploratory Factor Analysis (EFA) was used to identify latent constructs within the battery. The model constructed based on the EFA was evaluated in the validation sample using Confirmatory Factor Analysis (CFA), and reliability and validity were assessed for the final measure. The EFA in the calibration sample revealed an eight factor solution, and a final model with one second-order factor along with the eight first-order factors provided the best fit. The model combined items from each of the four parent measures, showing important relationships among the parent measures. When the model was fit using the validation sample, the results confirmed the validity and reliability of the model. A brief PRO for MS (BPRO-MS) that combines MS-related psychosocial and quality of life domains can be used to assess overall functioning in mildly disabled MS patients.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that can impact physical, cognitive, psychological and social functioning (Olascoaga, 2010; Rothwell et al., 1997; Vickrey et al., 1995). Although clinical exam measures provide a direct assessment of the state of a patient, patient-reported outcomes (PROs) are an important tool for assessing the disease from the patient's perspective (Fayers and Machin, 2007; Solari, 2005; Whitaker et al., 1995). Numerous measures have been developed to assess a range of domains including quality of life (QOL), depression, fatigue and social support, and each of these domains represent important features of the overall functioning of MS patients. Unfortunately, the myriad of PRO measures assessing similar domains has led to confusion with respect to selection and interpretation of findings (Baumstarck et al., 2013; Choi et al., 2014; Devy et al., 2013). Although the scales are trying to measure separate underlying features of the patient, several items across questionnaires appear to be measuring similar domains. For example, "I have been forgetful" from the Modified Fatigue Impact Scale (MFIS) appears to be measuring the same domain as "Have you had trouble with your memory?" from the Multiple Sclerosis Quality of Life – 54 (MSQOL-54), with both items assessing subjective memory complaints. As another example, both "I felt I could not shake off the blues even with the help from my family and friends" from Center for Epidemiologic Studies Depression Scale (CES-D) and "Have you felt so down in the dumps that nothing could cheer you up?" from MSQOL-54 seemed to target an overlapping domain. Since perceived social support has been shown to be associated with physical activity, depression and quality of life in MS patients (Motl et al., 2009), the Medical Outcomes Study (MOS) Modified Social Support Survey (MSSS) is also of interest in this study. In addition, psychometricians over the

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past several decades have emphasized that questionnaires intended for use in clinical populations should be as brief as possible in order to minimize respondent burden (Skevington et al., 2004; Sloan et al., 2002). For MS patients in particular, reduced attention and concentration could impair a patient's ability to complete long PRO batteries (Gold et al., 2001). Hence, a brief and valid tool for PRO assessment combining items across the existing PRO measures would be of interest if most of the information from the original scales could be maintained.

To address the problems associated with multiple measures of similar domains, several authors have investigated the relationship between items from multiple scales. Amtmann et al. evaluated the psychometric properties of three depression scale scores, the (a) PHQ-9, (b) CESD-10 and (c) eight-item PROMIS Depression Short Form, and the authors reported that the measure's one factor model was invariant as evidenced by the confirmatory factor analysis (CFA) (Amtmann et al., 2014). Devy et al. investigated items from the MSQOL-54 and other measures to develop a 10-item brief measure of quality of life (Devy et al., 2013). Miller and Dishon evaluated the factor structures of the MSQOL-54 and the Fatigue Severity Scale (FSS) within an Israeli MS population (Miller and Dishon, 2005).

Although previous studies have assessed the relationships among items across multiple measurements, no study has investigated the relationships among a set of measures of quality of life, fatigue, depression and social support using data from a large, well-characterized MS cohort. The purpose of this study was to evaluate the associations between items from a standard battery of PRO measures used in MS research and to develop a brief, reliable and valid measure by combining these items into a single measure.

Table 1
Demographic characteristics of study subjects.

N	537
Age (years, mean (SD))	46.45 (11.23)
Disease duration (years, mean (SD))	13.54 (7.95)
% Of males	26.8
Race (%)	
Asian	0.56
Black/African–American	2.61
More than one race	1.86
White	94.22
Unknown or not reported	0.75
Ethnicity (%)	
Hispanic or latino	3.54
Non-Hispanic or latino	96.28
Unknown or not reported	0.19
Disease category (%)	
RRMS	79.81
PPMS	4.3
SPMS	10.47
PRMS	0.19
CIS	5.23
EDSS (median, IQR, range)	1.50 (0.00, 2.50, 0.00 – 8.50)
% treated	78.77

RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PRMS: primary relapsing multiple sclerosis; CIS: clinically isolated syndrome; EDSS: expanded disability status scale.

2. Methods

2.1. Subjects

Subjects were selected from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital, Partners MS Center (CLIMB) study (Gauthier et al., 2006). This study was approved by the Partners Humans Research Committee and informed consent was obtained according to committee guidelines. Inclusion criteria for the CLIMB study are age ≥ 18 years and a clinically isolated syndrome (CIS) or diagnosis of MS (Polman et al., 2005). All subjects have clinical visits every six months after their enrollment date that include complete neurological exams and Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983). A subset of subjects also completes PRO measures biennially, and the battery was updated in 2009 to include additional measures. For each subject, the most recent clinical visit after 2009 with complete associated questionnaire data was used for analysis. A total of 608 subjects were eligible to contribute to this study. Because subjects were required to have complete data on all items from each questionnaire, 71 subjects were removed from the analysis due to missing data. Therefore, our final sample was 537 subjects. Demographic and clinical characteristics of subjects are provided in Table 1.

2.2. Measures

PRO measures included in our analyses were the Multiple Sclerosis Quality of Life-54 (MSQOL-54) (Vickrey et al., 1995), Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994) and MOS Modified Social Support Survey (MSSS) (Rao, 1992). The MSQOL-54 is a 54-item questionnaire that includes the MOS Short-Form Health Survey (SF-36) (Ware and Sherbourne, 1992) and 18 MS-specific items. CES-D is a 20-item measure of depressive (Radloff, 1977), MFIS is a 21-item fatigue scale (Amtmann et al., 2012; Fisk et al., 1994), and MSSS is an 18 item social support scale.

2.3. Statistical analysis

We randomly split our sample of 537 subjects into two datasets of approximately equal size via the SURVEYSELECT procedure in SAS 9.3 (Cary, NC), so that we could build the model in the first dataset (calibration sample) and test the validity of the model in the second dataset (validation sample). With the calibration sample, we performed item reduction followed by an exploratory factor analysis (EFA). Item reduction was conducted by first examining the Pearson's correlation coefficient matrix. Items were flagged for deletion if the inter-item correlation was ≥ 0.80 (Costello and Osborne, 2005). To choose between the duplicated items, we assessed the content of each item, and the items included in the subsequent analysis were chosen based on the opinion of our team's neuropsychologist (BIG).

2.3.1. Exploratory factor analysis

Then, we conducted an EFA using principal axis factoring with the promax oblique rotation method (Costello and Osborne, 2005; Henson and Roberts, 2006; Meyers et al., 2012). The final factor structure was determined by inspection of the scree plot, Kaiser–Guttman's eigenvalue > 1.0 rule, inter-factor correlations, proportion of common variance explained and overall factor structure interpretability. Items with high factor loading for each factor (≥ 0.5) were identified as potential items for further inspection. Because a goal of the analysis was to develop a parsimonious measure, we chose to retain the three items with the highest loadings from the EFA for each factor since a minimum of three